Long-term side effects of adjuvant breast cancer treatment

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Chapter 4

Hot flashes in breast cancer patients

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ABSTRACT

Objectives

A literature search was conducted to gather information concerning the pathophysiologic mechanisms leading to hot flashes, their prevalence and severity in breast cancer patients, their influence on quality of life, and the best therapeutic option.

Methods

Relevant studies in English were selected from Medline.

Results and conclusion

Pathophysiologic mechanisms leading to hot flashes are poorly understood. Estrogen withdrawal is considered to have a central role. Also, serotonin and norepinephrine seem to be involved in hot flash induction. Menopause induced by chemotherapy or ovarian ablation, is accompanied by an abrupt decrease in estrogen level, causing vasomotor symptoms. Hot flashes are also a side effect of tamoxifen and aromatase inhibitors. Quality of life in breast cancer patients may be negatively influenced by hot flashes, and therefore, adequate treatment is important. Currently, of the several non-hormonal options, the selective serotonin-reuptake inhibitor (SSRI) venlafaxine is the most effective in breast cancer patients. However, studies on interaction between SSRIs and tamoxifen may influence future recommendations.

INTRODUCTION

Hot flashes are common in post- and perimenopausal women. In women treated for breast cancer, the prevalence of vasomotor symptoms is higher than in healthy women, and hot flashes often occur at a younger age. As a growing number of women receive adjuvant chemotherapy and/or endocrine therapy for their breast cancer, and as more women survive breast cancer nowadays, treatment of hot flashes in these patients becomes increasingly important. Treatment options, however, are limited.

In healthy women with hot flashes, hormonal therapy with estrogens, either combined with or without progestagens, is very effective in reducing bothersome hot flashes, but has been under fire lately. This is due to small, but significant, increases in the risks of coronary events, stroke, pulmonary embolism and breast cancer associated with hormone replacement therapy in healthy, postmenopausal women.[1,2] Especially combinations of estrogen and progestagen are associated with a higher risk of breast cancer.[1-3] Because of the concerns about the influence of hormones on breast cancer, estrogens and estrogen-progestagen combinations are regarded to be contraindicated in breast cancer patients. Safe alternatives are needed to adequately treat hot flashes in these women. Over the last decades new drugs for alleviating vasomotor symptoms have emerged with marked differences in efficacy and side effects.

Apart from the therapeutic considerations, there is still much to be learnt about the mechanisms responsible for the development of hot flashes and the associated risk factors. Furthermore, despite the prevalence of hot flashes, little is known about their influence on quality of life.

METHODS

Study objectives

The purpose of this paper is fourfold. The first objective is to describe the pathophysiologic mechanisms leading to hot flashes, the second to give an explanation for the prevalence of more frequent and more severe hot flashes in patients treated for breast cancer, the third objective is to describe the influence of hot flashes on quality of life in these patients, and the last is to describe the currently most effective, best tolerated, and also safe, drug options for the treatment of hot flashes in women with a history of breast cancer.

A literature search was conducted to find appropriate data with respect to these objectives. In order to provide the necessary background information, literature was additionally searched for data about menopause and vasomotor symptoms in healthy women.

Data sources and study selection

Relevant studies were identified by using the Medline database. Literature from the period 1977-2005 and written in English was searched with the search terms: hot flushes, hot flashes (used in American literature), menopause, pathophysiology, quality of life, breast cancer, chemotherapy, endocrine therapy, tamoxifen, ovarian ablation, LHRH analogues, hot flash therapy, hormonal replacement therapy, estrogen, progestagen, clonidine, SSRI, venlafaxine, fluoxetine, paroxetine, vitamin E, phytoestrogen, gabapentin, bellergal, black cohosh. These search terms were used in varying combinations to identify the most suitable literature for this paper. Also, reference lists of selected papers were used to find articles that did not appear in the primary search.

Studies were selected if they were original papers or reviews. Large randomized, double-blind, placebo-controlled trials were preferable to small, non-placebo-controlled trials. However, the use of small, non-controlled studies was not always avoidable, due to the limited amount of literature with respect to certain subjects. For example, for some drugs no large comparative trials have (yet) been conducted. Case reports were excluded. Studies were used if they were relevant in serving the objectives of this paper.

RESULTS

Menopause

Hot flashes occur as part of the symptom complex associated with menopause. Menopause is being defined as the permanent cessation of menstruation due to ovarian failure and marks the end of a woman's reproductive life. The postmenopausal date can only be determined retrospectively, as a period of 12 months of amenorrhea has occurred. Women in whom the ovaries have been removed are considered postmenopausal as well. Perimenopause corresponds to the period of transition from regular menstruation to its cessation. Perimenopausal status in women can be further defined as being late perimenopausal: menstruation has occurred in the past 12 months, but not in the last 3 months; and early perimenopausal: menstruation has occurred in the

last 3 months, but has become less predictable.[4-6] The average age of menopause in Western countries is about 50-51 years.[7]
Menopause is the result of exhaustion of follicles in the ovaries and is accompanied by changes in hormone levels. The decreasing excretion of estrogens results in the loss of negative feedback and an increasing production of gonadotropins. High levels of circulating follicle-stimulating hormone (FSH) and low levels of estradiol (E2) are typical of menopause.[8] When women become postmenopausal, they may experience several symptoms associated with estrogen deficiency or withdrawal, including hot flashes, night sweats, palpitations, urinary incontinence and vaginal dryness. Hot flashes are among the earliest symptoms of menopause and most frequently experienced.[5]

Hot flashes

A hot flash is characterized by the sudden onset of a sensation of intense warmth that begins in the chest and may progress to the neck and face.[8] Hot flashes, or vasomotor symptoms, are generally associated with objective vasodilatation and a drop in core body temperature. They may be accompanied by sweating, flashing, palpitations, anxiety, irritability and are sometimes followed by chills.[9] Sleep disturbances may occur in women who have hot flashes at night.[10] The average hot flash lasts about 4 minutes, but it can last a few seconds or as long as 20 minutes.[9,11] Some women experience a few hot flashes per week, whereas others report having hot flashes as often as twice per hour.[9,12]

Pathophysiology of hot flashes

The underlying pathophysiologic mechanisms of hot flashes in postmenopausal women are not well understood.[8] The occurrence of hot flashes is concordant with hormonal changes at the time of menopause. Hot flashes are considered to be secondary to changes in estrogen levels. Rather than absolute low levels of circulating estrogen, estrogen withdrawal is thought to be the instigator for hot flashes.[13] This is consistent with the finding that women experience hot flashes when they become postmenopausal, and that hot flashes resolve after a period of time despite continuing low levels of estrogen.[9] However, the exact mechanism of how a decrease in estrogen leads to the development of hot flashes is unclear.
Changes in estrogen levels may affect the functioning of the thermoregulatory centers in the hypothalamus.[9] Central thermoregulatory centers maintain core body temperature within a normal range (the thermoneutral zone). If the body temperature exceeds the upper threshold, perspiration and peripheral vasodilatation occur. A body temperature under the lower threshold induces

shivering.[14] In postmenopausal women with hot flashes the thermoneutral zone is virtually non-existent, in contrast to asymptotic women, who have a normal thermoneutral zone of 0.4°C. In a study among 12 postmenopausal women reporting frequent hot flashes and seven women reporting none, the core body temperature "sweating threshold" was lower in the symptomatic postmenopausal women than in the postmenopausal women without hot flashes.[15]

Thermoregulatory centers seem to be influenced by changing estrogen concentrations. This proceeds by direct or indirect pathways. The indirect pathways may act through changes in neurotransmitter levels. The primary neurotransmitters involved in thermoregulation are norepinephrine and serotonin (5-HT). Both may be responsible for lowering the temperature setpoint and inducing heat loss mechanisms.[13,16] In animal studies, increased hypothalamic norepinephrine levels narrow the thermoneutral zone and decreased hypothalamic norepinephrine levels widen it. In a blind, placebo-controlled study by Freedman et al. clonidine, an α_2-adrenergic agonist, which has been shown to lower hypothalamic norepinephrine levels, raised the sweating threshold in symptomatic postmenopausal women.[15] This supports the hypothesis that increased brain norepinephrine levels narrow the thermoneutral zone and contribute to the initiation of hot flashes.[14-16]

Serotonin may be important in the pathophysiology of hot flashes as well, but its role is more complex. Evidence from animal studies leads to the assumption that the balance between two serotonin receptor subtypes, 5-HT1a and 5-HT2a, influences thermoregulation.[17-19] Stimulation of the 5-HT2a receptor induces hyperthermia, whereas administration of 5-HT1a receptor agonists lowers the body temperature. Gonadal hormones, especially estrogen, affect expression and activity of 5-HT receptors in direct or indirect, yet unknown, ways.[9]

The exact trigger that sets off the mechanism leading to a hot flash is not known. Small elevations in body temperature precede most hot flashes.[20-22] These subtle increases in body temperature, combined with a narrow thermoneutral zone, may trigger heat loss mechanisms, including vasodilatation and subsequent flashing and sweating, thus, symptoms matching a hot flash.

Hot flashes in healthy women

In healthy peri- and postmenopausal women the prevalence of hot flashes varies from 24 to 93%.[12] This wide range is due to several factors, including unequal study populations, varying research methods and dissimilar definitions of hot flashes and menopausal status. Hot flashes usually start 1 to 2 years before menopause and persist for 6 months to 5 years thereafter.[8] The prevalence of flashing is highest in late perimenopausal and postmenopausal women.[6,12] The occurrence of vasomotor symptoms depends on various factors. In a large,

community-based study in the United States among 16,065 women, aged 40-55 years, and belonging to five different ethnic groups, the relation between menopausal symptoms and demographic and lifestyle factors was investigated.[6] Women were interviewed about the presence or absence of vasomotor, physical and psychological symptoms in the previous 2 weeks. African American women reported more hot flashes than Caucasian women (45.6% and 31.2% respectively). Hot flashes were reported least frequently by Japanese and Chinese women (17.6% and 20.5% respectively). Besides ethnic background, socio-economic status and lifestyle influenced menopause-related symptoms. Lower educational level, difficulty in paying for basic needs, smoking, less physical activity and a higher body mass index were associated with hot flashes. Although this study is one of the largest studies concerning menopausal symptoms in midlife women, limitations lie in its cross-sectional design and methods of data acquirement (self-reported as opposed to direct measurement). In a cross-sectional study the temporal sequence of associations cannot be established. Therefore, the causal relation in, for example, the occurrence of vasomotor symptoms in women who are less physically active cannot be determined. Physical activity may protect against hot flashes, but hot flashes may also be the cause of decreased physical activity in women suffering from them. The same applies to the association between a high body mass index and a greater prevalence of hot flashes. Also, information acquired by self-reporting may not be completely accurate, for instance with respect to body mass index and menstrual status.

There is a discrepancy in results from this large (n = 16,065), cross-sectional study compared to some other studies. The finding that a high body mass index is related to more hot flashes is confirmed by a couple of studies[23,24], yet others describe the opposite, namely that a lower body weight is a risk factor for vasomotor complaints.[25-27] The explanation for this last observation is the reduced conversion of androgens into estrogens in peripheral fat in slim women. Despite the limitations, results from this study are valuable, because of the large sample size and the acquirement of data among women from diverging socio-economic and ethnic backgrounds.

A community-based study in Sweden among 6,917 women, aged 50-64 years, confirmed the association between a lower educational level, a lower socio-economic status, smoking, and the occurrence of more hot flashes.[24] The consumption of large amounts of alcohol was also associated with more vasomotor symptoms. Physical activity on the other hand reduced the prevalence of hot flashes.

Hot flashes in breast cancer patients

Breast cancer

Breast cancer is the most common cancer in women. One out of every nine women will be confronted with breast cancer during her life. Treatment of breast cancer includes surgery, and in addition, radiotherapy and/or adjuvant systemic therapy. Adjuvant systemic therapy consists of chemotherapy, endocrine therapy or a combination of both. Patients receive adjuvant systemic therapy depending on their age, the size of the tumor, the differentiation grade, the hormone-receptor status and the nodal involvement.

Hot flashes in breast cancer patients

Studies conducted to determine the prevalence of hot flashes in postmenopausal breast cancer patients report a rate of 65%.[28-30] Couzi et al. studied the prevalence and severity of menopausal symptoms among 190 postmenopausal breast cancer patients, aged 40-65 years.[30] About two thirds of the women reported hot flashes; 29% of these women rated their hot flashes as mild, 37% as moderate and 34% as severe.

Carpenter et al. observed a hot flash prevalence of 65% out of 114 postmenopausal women treated for breast cancer (mean age 58.8 years).[28] All patients had completed their primary breast cancer treatment (surgery, radiotherapy and/or chemotherapy) at least 3 months before entering the study. Tamoxifen was used by 47% of the women, and for 57% of these patients tamoxifen was the only adjuvant therapy they received. Of the 74 breast cancer patients reporting hot flashes, 59% rated their symptoms as severe, which is twice the number of naturally postmenopausal, healthy women experiencing severe hot flashes (approximately 25%).[12] Hot flashes occurred in 72% of the tamoxifen users and in 78% of the women treated with chemotherapy. Therefore, the prevalence rate of certain subgroups of postmenopausal breast cancer patients may be even higher than the prevalence of vasomotor symptoms in the whole group of breast cancer patients.[28] In this study no data were reported about the mean age in either subgroup. Also, no information was offered concerning the number of women who received tamoxifen after chemotherapy; there may have been some overlap in both groups.

Another study compared the occurrence of hot flashes in 69 breast cancer survivors (mean age 57 years) with age-matched healthy women.[29] Of the women with a history of breast cancer 65% experienced hot flashes, whereas this was 16% for the healthy women. The hot flashes in breast cancer patients were also rated as more severe. However, although the groups were matched for

age, they were not matched for menopausal status, and in fact, 93% of the women treated for breast cancer was either peri- or postmenopausal, compared to 81% of the healthy women. The other women included in the study were premenopausal and therefore not likely to experience menopausal symptoms.
Based on these studies, the prevalence of hot flashes is higher in postmenopausal women treated for breast cancer than in healthy postmenopausal women, and breast cancer patients experience more severe vasomotor symptoms. Moreover, hot flashes appear to last longer in breast cancer patients. Of the women who were postmenopausal for more than 10 years, 54% still experienced hot flashes, which is significantly more than the 4-35% rate found in healthy women.[12,28]

Adjuvant chemotherapy

Adjuvant polychemotherapy improves the 10-year survival of women aged under 50 with early breast cancer with 7-11%.[31] However, a long-term side effect of this treatment is an earlier onset of menopause and menopausal complaints. Cytotoxic agents induce ovarian damage, ranging from a decreased number of follicles to absent follicles with ovarian fibrosis.[4] Clinically, this is characterized by oligomenorrhea, amenorrhea and menopausal symptoms.
Bines et al. reviewed the effect of adjuvant chemotherapy for breast cancer on the ovarian function in premenopausal women.[4] Chemotherapy-related amenorrhea in regimens based on cyclophosphamide, methotrexate and fluorouracil (CMF) given for a period of at least 3 months is about 68%, with a range of 20% to 100%. This wide range is due to the various definitions of amenorrhea and menopausal status, the age of the patients, and the cumulative dose, duration and route of administration of the chemotherapy. Incidence of amenorrhea in the group treated with doxorubicin and cyclophosphamide (AC) was 34%, which was lower than the incidence of chemotherapy-related amenorrhea after treatment with CMF.[4] In another study, no difference was observed in the risk of development of menopause following CMF or a regimen with cyclophosphamide, epirubicine and fluorouracil (CEF).[32]
In women who are treated with chemotherapy, the mean age at which menstruation ceases varies from 38 to 46 years; 4-13 years before the average age of menopause in healthy women.[4] Age is a determining factor for the occurrence of ovarian damage with chemotherapy. Patients older than 40 years have a higher incidence of chemotherapy-related amenorrhea than patients younger than 40 years (40% vs. 76%). In younger women, higher cumulative doses of chemotherapy are needed for inducing ovarian failure. This age-related effect is most likely the result of the lower number of follicles present in the ovaries of older women.[4]

The onset of menopause due to chemotherapy can be sudden and premature. The subsequent abrupt drop in estrogen levels (as opposed to the more gradual decrease in natural menopause) may account for the greater frequency and severity of hot flashes in breast cancer patients.[28,33]

Adjuvant endocrine therapy

Tamoxifen

Adjuvant therapy with tamoxifen for 5 years improves the disease-free and overall survival of patients with hormone receptor-positive breast cancer.[34] Tamoxifen can exert an anti-estrogenic effect as well as an estrogenic effect, depending on the ambient serum estrogen levels in women (the menopausal status) and on different sites and tissues. In breast tissue tamoxifen acts as an estrogenic antagonist.[35] Hot flashes are a main side effect of tamoxifen. In a study of 98 women aged under 56 years, who received tamoxifen after either high-dose or standard-dose chemotherapy, 85% reported hot flashes.[10] This was unrelated to treatment arm. In the previously mentioned study by Couzi et al. the prevalence rate of hot flashes in the group of tamoxifen users was higher than in nonusers (78% vs. 59%).[30] Furthermore, the women receiving tamoxifen reported more severe hot flashes. In a double-blind, randomized study among 2,644 breast cancer patients, receiving either tamoxifen or placebo, more hot flashes were reported by the women using tamoxifen (57%) compared to the women in the placebo group (40%).[36] A cohort study evaluated the use and side effects of adjuvant tamoxifen among 303 women aged 55 years or older. In this study, patients who experienced side effects were more likely to stop taking tamoxifen.[37]

LHRH analogues

Whereas tamoxifen inhibits the effect of the circulating estradiol, estrogenic effects on breast cancer can also be prevented by eliminating estrogen production. In premenopausal women the ovarian production of estradiol can be diminished either surgically, by removal of the ovaries, or medically, using luteinizing hormone releasing hormone (LHRH) analogues. Ovarian ablation as adjuvant treatment has a substantial survival benefit in women under 50 years.[38] LHRH analogues pursue the same hormonal effects as surgical ovarian ablation without the irreversibility and risks associated with the latter. LHRH analogues act on the hypothalamic-pituitary axis. Initially, FSH and luteinizing hormone (LH) levels will increase shortly, but with continuing use of LHRH analogues, the pituitary gland becomes desensitized in about 2 weeks. This means that receptor down-regulation takes place, leading to the inhibition of FSH and LH release and consequently, to ovarian suppression with a decrease in estrogen

levels.[39] LHRH analogues have obtained a larger role in the treatment of breast cancer in recent years, and are increasingly being added to tamoxifen in the adjuvant setting in premenopausal women. Because these drugs are to be used for several years, the side effects caused by LHRH analogues deserve attention.
The ZEBRA trial, a prospective study in 1,614 patients, showed an equal efficacy of goserelin (an LHRH analogue) for 2 years and 6 cycles of CMF chemotherapy in pre- and perimenopausal women with node positive, hormone-receptor positive, early breast cancer.[40,41] Patients treated with goserelin did not have the acute side effects of chemotherapy, such as nausea, vomiting, alopecia and increased risk of infection, but they did experience more menopausal symptoms, including hot flashes and vaginal dryness. However, in the goserelin group the menopausal symptoms improved after cessation of the therapy, whereas in the patients treated with CMF these complaints remained.
In a trial in 149 premenopausal breast cancer patients, randomized in four groups receiving goserelin, tamoxifen, goserelin plus tamoxifen or no systemic therapy (control group), the effects of adjuvant endocrine therapy on physical and psychological symptoms were studied. The patients who received tamoxifen alone reported more hot flashes than the control group. Patients in the goserelin and in the combination group, however, reported the highest levels of vasomotor symptoms probably due to the abrupt menopause caused by the LHRH analogue.[39]

Aromatase inhibitors
Aromatase inhibitors inhibit the conversion of androgens into estrogens in muscle and peripheral adipose tissue. In postmenopausal women the main source of estrogens is adipose tissue. In the adjuvant setting, the use of aromatase inhibitors for the treatment of postmenopausal women with breast cancer has been studied. The ATAC trial, a large study among 9,366 breast cancer patients, compared treatment with anastrozole (an aromatase inhibitor), tamoxifen and both anastrozole and tamoxifen in postmenopausal women in terms of efficacy and side effects.[42] Disease-free survival after 4 years was better with anastrozole than with tamoxifen or the combination of anastrozole and tamoxifen. Of the patients receiving anastrozole 35.0% reported hot flashes compared to 40.3% for tamoxifen and 40.7% for the combination. Quality of life was similar in the three treatment arms.[43]
In a recent study 4,742 breast cancer patients were randomized to receive either 5 years of tamoxifen as adjuvant therapy or exemestane, a steroidal aromatase inhibitor, after 2-3 years of tamoxifen.[44] No difference was seen in the occurrence of hot flashes between both groups; 42.0% of the patients in the exemestane group and 39.6% in the tamoxifen group reported hot flashes.

A randomized trial in 5,187 postmenopausal women receiving either letrozole, an aromatase inhibitor, or placebo after 5 years of treatment with tamoxifen for breast cancer, showed a higher prevalence of hot flashes in the letrozole group (47.2% vs. 40.5% in the placebo group).[45] Of the patients in the letrozole group, 4.5% discontinued the medication due to side effects and of the women receiving placebo 3.6%, which was a non-significant difference. These last two studies showed an improved disease-free survival with aromatase inhibitors after treatment with tamoxifen.
Summarizing, in women with a history of breast cancer, vasomotor complaints are often exacerbated due to several reasons. First, chemotherapy and ovarian ablation in premenopausal woman can induce abrupt menopause with marked symptoms. Second, tamoxifen and aromatase inhibitors are commonly used as adjuvant therapy in breast cancer, with hot flashes as a frequently occurring side effect.

Quality of life

Quality of life is a broad concept, including physical, emotional, social, cognitive and sexual functions, as well as symptoms related to disease and treatment. These aspects are considered from the patient's point of view. Quality of life has become an important factor in evaluating treatment efficacy.[46] The occurrence of hot flashes may have an influence on a woman's quality of life.
In an early and small study, a questionnaire-based interview on quality of life was conducted among 63 healthy women (i.e. with no history of breast cancer) aged 45-60 years. Menopausal symptoms in these women were associated with a compromised quality of life. Quality of life improved in women receiving hormone replacement therapy.[47] However, recently a very large, randomized, placebo-controlled study evaluating the effect of estrogen plus progestin on health-related quality of life among 16,608 healthy, postmenopausal women, reported no clinically meaningful effects of the therapy on quality of life.[48] In this study, quality of life was assessed using several questionnaires, including the RAND-36, which were completed at baseline and one year after randomization. Menopausal symptoms were assessed as well. In addition, 1,511 women provided data concerning health-related quality of life after 3 years. No differences between the estrogen-plus-progestin group and the placebo group were observed after 3 years either. In the subgroup of women aged 50-54 years with moderate to severe vasomotor symptoms, those who had received estrogen and progestin for a year experienced an improvement in the severity of hot flashes and less sleep disturbances, but surprisingly, no positive effects on quality of life were seen. This trial was, however, not designed to study the effects of hormone therapy on hot flashes. The majority of the women

participating in the trial did not experience vasomotor symptoms and those who did, were not likely to be very much bothered by the flashes, since they knew they could be randomized to receive placebo.[49]

Carpenter et al. addressed the relationship between hot flashes and quality of life among breast cancer patients, using a questionnaire directed at the influence of hot flashes on functional status.[28] Of the 114 women participating in the study, 74 reported hot flashes. The prevalence and severity of hot flashes were marginally related to decreased physical and mental quality of life. More recently, they studied the influence of hot flashes on mood, daily activities and overall quality of life in 69 women with a history of breast cancer and 63 age-matched healthy females.[29] Women with a history of breast cancer reported greater interference with daily activities and quality of life than healthy women. Breast cancer patients with daily hot flashes experienced a moderate to severe impact of hot flashes on sleep, concentration, mood and sexual functioning. Furthermore, compared to breast cancer patients without or with mild hot flashes, breast cancer patients with severe hot flashes showed greater mood disturbance, greater interference with daily activities, including sleep, concentration and sex, and a poorer quality of life.

Stein et al. studied the impact of hot flashes on quality of life among postmenopausal breast cancer patients through self-report questionnaires.[50] Of the 70 eligible women 28 (40%) had hot flashes. Women experiencing hot flashes reported higher levels of fatigue, poorer sleep quality and poorer physical health than women without flashes. These differences remained significant even after adjustments for the medical, demographic and treatment variables. Severity of hot flashes was negatively associated with quality of life. Women with moderate or severe hot flashes experienced more fatigue and poorer physical health than women with mild hot flashes. The women with vasomotor symptoms did not differ from the group without flashes in terms of mental health or levels of anxiety or depression. Limitations of this study are the relatively small sample size, the rather homogeneous sample of mostly Caucasian, middle class and fairly well-educated women and the use of data concerning the prevalence and severity of hot flashes from a single assessment instead of gathering this information throughout the course of treatment.

In a study analyzing tamoxifen effects on subjective and psychosexual well-being in breast cancer patients after high-dose and standard-dose chemotherapy, a strong relation was seen between hot flashes and disruption of sleep and also an association with difficulty concentrating.[10] Irritability was related to concentration problems and disturbed sleep. Decreased sexual desire was reported by 44% and related to vaginal dryness (40%) and dyspareunia

(30%). No differences were seen between the high-dose and standard-dose groups.
Although relatively few studies researching this matter have been conducted so far, there appears to be a negative influence of hot flashes on quality of life in breast cancer patients.

Treatment of hot flashes

In post- and perimenopausal healthy women hot flashes can be treated with systemic hormonal therapy (estrogen alone or combined with progestagen).[51] Estrogen therapy decreases hot flashes by 80%-90% and is considered to be the most effective form of treatment for menopausal symptoms.[8] Because of the associated breast cancer risk, at the moment the only indication for hormonal substitution therapy in healthy, postmenopausal women is hot flashes that severely compromise quality of life. One could consider the use of systemic hormonal therapy in a selected group of hormone-receptor negative breast cancer patients suffering from severe vasomotor symptoms resistant to non-hormonal therapies. Little is known about the effects of systemic hormonal therapy in this selected population. However, because of the increased risk of developing a second primary breast tumor in women with a history of breast cancer[52], hormonal therapy does not seem appropriate, even in a selected group of patients. Also, tamoxifen reduces the rate of contralateral breast cancer, when given as adjuvant treatment of early breast cancer, suggesting a role for estrogen in the development a second primary breast tumor.[53] In general, systemic hormonal therapy is considered to be contraindicated in breast cancer patients.[54]

Placebo effect

Placebo-controlled trials have shown a substantial placebo-effect in the treatment of hot flashes. Therefore, when the effectiveness of medication for the treatment of hot flashes is being evaluated, this placebo-effect must be taken into account.[33] The placebo-effect in trials amounts to a reduction in hot flash frequencies and scores as high as 20%-30% over a period of 4 weeks.[55-59] In a series of 968 patients in seven trials, a minority of the patients on placebo (15%) reported a profound decrease in hot flash activity, i.e. a more than 75% reduction.[60] About 25% of the patients who received a placebo reported a reduced hot flash activity of at least 50%. The improvement of hot flashes in women on placebo was seen in studies using self-report diaries as a means to acquire data concerning hot flash frequencies and severity. This improvement may be the result of a true placebo-effect, but reduced compliance in self-reporting over time may also contribute to the observed effect.

Progestational agents

Megestrol acetate is a progestational agent that may be used as palliative therapy in breast cancer, but it is also used for the treatment of hot flashes (Table 1). In a double-blind, randomized, placebo-controlled trial with a cross-over design, megestrol acetate 20 mg twice daily was effective for the treatment of hot flashes.[61] A total of 97 women with a history of breast cancer were included. After an one-week pre-treatment observation period patients received megestrol acetate for 4 weeks, followed by 4 weeks of placebo or vice versa. Megestrol acetate reduced the frequency of hot flashes with 74% compared to baseline values, while in the placebo group a reduction of 27% was observed. An improvement was also visible in the hot flash score. This score takes into account the severity of the flashes, and is calculated by multiplying the number of hot flashes with points given for their severity and then adding up the results. In this study the reduction in hot flash score was 83% for megestrol acetate and 27% for placebo. The observed effect of megestrol acetate on hot flashes is similar to the effect reported with estrogen therapy.[8] Also, in this study, it became apparent that it takes approximately 2-3 weeks before a maximum effect is achieved and that, even after discontinuation of the medication, the effect lasts for a few weeks. In the study arm in which megestrol acetate was followed by placebo, flashes did not increase in frequency and severity until 2-3 weeks after the switch. An unexpected finding was a marked increase in hot flash scores after megestrol acetate was started in women who were concomitantly receiving tamoxifen; this effect lasted only a few days and was followed by a decrease. In this study, possible long-term side effects were not examined.[61]

A subsequent study evaluating the long-term use of megestrol acetate, showed that almost a third of the women continued to use megestrol acetate after 3 years, but that most women had lowered the dose.[62] Although low-dose megestrol acetate appeared to be well tolerated, there were some side effects. The reported side effects included vaginal bleeding, appetite stimulation, weight gain, episodes of chills and symptoms suggestive of carpal tunnel syndrome.

Another progestagen, medroxyprogesterone, is administered orally or as a depot by intramuscular (im) injection. In a small study, 15 women with a history of breast cancer were treated with 500 mg depot medroxyprogesterone acetate im every 2 weeks for a period of 6 weeks.[63] There was an approximate 90% decrease in hot flashes. The improvement persisted for months after discontinuation of treatment. These results, however, should be interpreted with great caution, because of the small sample size and the fact that the study is not a placebo-controlled, randomized trial. A randomized trial in 71 postmenopausal breast cancer patients, comparing 500 mg depot

medroxyprogesterone acetate im injections biweekly with 40 mg oral megestrol acetate daily showed a 86% reduction of hot flashes after 6 weeks, without significant differences between both groups.[64] An assessment after 24 weeks showed a better maintenance of response (without further treatment) in patients who received im depot medroxyprogesterone acetate (89% vs. 45%).

Table 1. Overview of clinical trials concerning treatment of hot flashes

Medication	Agent	Studies	Study agents
Progestational	Megestrol acetate	Loprinzi et al. 1994[61]	Megestrol acetate vs. placebo
	Medroxyprogesterone	Barton et al. 2002[63]	Medroxyprogesterone (im)
		Bertelli et al. 2002[64]	Medroxyprogesterone im vs. oral
	Progesterone cream	Leonetti et al. 1999[65]	Progesterone cream (transdermal) vs. placebo
Bellergal	Belladonna and phenobarbital	Bergmans et al.1987[66]	Bellergal vs. placebo
Clonidine		Nagami et al. 1987[67]	Clonidine (transdermal) vs. placebo
		Goldberg et al. 1994[56]	Clonidine (transdermal) vs. placebo
		Laufer et al. 1982[68]	Clonidine (oral; different doses) vs. placebo
		Pandya et al. 2000[69]	Clonidine (oral) vs. placebo
SSRIs	Venlafaxine	Loprinzi et al. 1998[70]	Venlafaxine
		Loprinzi et al. 2000[58]	Venlafaxine (different doses) vs. placebo
		Barton et al. 2002[71]	Venlafaxine
	Fluoxetine	Loprinzi et al. 2002[72]	Fluoxetine vs. placebo
	Paroxetine	Stearns et al. 2000[73]	Paroxetine
		Stearns et al. 2003[74]	Paroxetine (two doses) vs. placebo
		Stearns et al. 2004[75]	Paroxetine (two doses) vs. placebo
Vitamin E		Barton et al. 1998[55]	Vitamin E vs. placebo
Phytoestrogens		Quella et al. 2000[59]	Phytoestrogens vs. placebo
		Van Patten et al. 2002[86]	Phytoestrogens vs. placebo
Black cohosh		Jacobson et al. 2001[88]	Black cohosh vs. placebo
		Pockaj et al. 2004[89]	Black cohosh
Gabapentin		Guttuso et al. 2003[57]	Gabapentin vs. placebo
		Pandya et al. 2004[93]	Gabapentin
		Pandya et al. 2004[94]	Gabapentin (two doses) vs. placebo

Transdermal progesterone cream, containing 20 mg progesterone per quarter teaspoon (which was the amount of cream that was applied on the skin daily), was used in a randomized, double-blind, placebo-controlled trial to evaluate its

effects on bone mineral density and menopausal symptoms in postmenopausal, healthy women.[65] At study entry, 69% of the women in the treatment arm and 55% in the placebo arm experienced hot flashes. An improvement or resolution of hot flashes was seen after 4 months in 83% of the women treated with progesterone cream and in 19% of the placebo group. Because the subjects only recorded whether hot flashes increased, remained the same, improved or stopped, no data concerning hot flash frequencies or hot flash scores could be obtained.

Despite the effectiveness of progestagens for the treatment of hot flashes, there is a hesitation to use a hormonal agent in breast cancer patients. Irrefutable data that progestagens enhance the risk of breast cancer recurrence are lacking. However, the Million Women Study, a recent study among more than a million healthy women aged 50-64 years, did show an additional, increased risk of breast cancer in women using estrogen-progestagen combinations compared to those using estrogen only, suggesting an influence of progestagens on cancer growth.[2] Therefore, progestagens are generally best avoided for the treatment of hot flashes in breast cancer patients.

Bellergal

During the 1970s and 1980s Bellergal, a combination of belladonna and phenobarbital, was widely used for the treatment of hot flashes in breast cancer patients.[8] A randomized, double-blind study of 38 women comparing Bellergal retard and placebo for a period of 8 weeks, showed a slight decrease in the hot flash frequency with Bellergal.[66] However, this effect lasted only for about 4 weeks. After 8 weeks there were no more differences between both groups. No data from other randomized, prospective studies have been published.

Because of the small and short-lived benefit of Bellergal and the risk of dependence on phenobarbital, Bellergal is not recommended for the treatment of hot flashes.

Clonidine

Clonidine is a centrally acting α_2-adrenerge agonist and is primarily used to treat hypertension. Clonidine can be administered transdermally or orally and appears to have an effect on the occurrence of hot flashes. A double-blind, randomized study in 30 postmenopausal women receiving transdermal clonidine at a rate of 0.1 mg/day or placebo for 8 weeks, showed a decrease of hot flashes with clonidine.[67] In the clonidine group 80% of the patients reported fewer hot flashes and in the placebo group 36%. The side effects of clonidine were minimal and restricted to transient local skin reactions.

More side effects and less impressive results with respect to efficacy were seen in a larger study with transdermal clonidine. A total of 110 breast cancer patients using tamoxifen were randomized to receive clonidine (0.1 mg/day) for 4 weeks, followed by 4 weeks of placebo or vice versa, in a double-blind, crossover study design.[56] Clonidine reduced the hot flash frequency 20% from baseline. This was more than the placebo effect, but still clinically rather modest. Furthermore, patients complained of several side effects, including dry mouth, constipation, drowsiness and dizziness.

An earlier study with clonidine given orally, was conducted among 10 healthy, postmenopausal women.[68] They received a placebo for 2 weeks, followed by clonidine 0.1, 0.2 and 0.4 mg, each dose for 2 weeks and in varying order. The women were blinded to the dose they received, the investigators, however, were not. Four patients withdrew due to side effects, three because of dizziness (two when receiving 0.2 mg and one when using 0.1 mg per day), and one stopped because of fatigue, nausea, headaches and irritability at 0.1 mg/day. In the six patients who completed the study, a reduction in the frequency of hot flashes was observed. Clonidine 0.4 mg/day resulted in a 46% decrease in hot flashes compared to 7% with placebo. Of these six patients, five complained of mouth dryness and two of insomnia. Although the sample size of this study is too small to draw definite conclusions with respect to efficacy, it can be concluded that clonidine may have some unpleasant side effects.

Oral clonidine was also used in a randomized, double-blind, placebo-controlled clinical trial to evaluate its effectiveness for the control of tamoxifen-induced hot flashes in 194 breast cancer patients.[69] The mean decrease in hot flash frequency after 8 weeks was larger with 0.1 mg clonidine per day than with placebo (38% vs. 24%). The women treated with clonidine reported more sleeping difficulties than the patients in the placebo group (41% vs. 21%). An improvement in the mean quality of life scores in the clonidine group was seen, as opposed to a small decrease in the placebo group. However, the median score in both groups was similar. In none of the above mentioned studies adverse events with respect to blood pressure were reported.

Recently, clonidine was found to raise the sweating threshold in symptomatic, postmenopausal women by Freedman et al.[15] As mentioned before, increased brain norepinephrine levels seem to play a role in the induction of hot flashes. Clonidine reduces central sympathetic activation and this may well be the pathway by which the drug exerts its action on flashes.

In summary, clonidine reduces the occurrence of hot flashes to some extent and can be used safely in women with a history of breast cancer. The positive effect on hot flashes was seen at doses lower than used for treatment of hypertension. However, the concurrent use of clonidine and certain other drugs may have

some unfavorable consequences. Clonidine enhances the effects of antihypertensives, anxiolitic drugs and, also, of alcohol. If clonidine is discontinued in patients using ß-blockers, rebound hypertension may develop.

Selective serotonin-reuptake inhibitors

Selective serotonin-reuptake inhibitors (SSRIs) belong to a group of newer antidepressants. In the 1990s anecdotal evidence emerged for the reduction of hot flashes in women treated with SSRIs for depression. Theoretically, SSRIs were also expected to have an effect on flashes, because of the role of serotonin in the pathophysiology of hot flashes. SSRIs block neuronal serotonin (5-HT) reuptake, resulting in higher serotonin concentrations in the synapses. This induces both down- and upregulation of different 5-HT receptors in the central nervous system, including 5-HT1a and 5-HT2a, and subsequent changes in the balance between the receptors. The hypothalamic thermoregulatory centers are affected as well, and this may account for inhibition of flashes by SSRIs.[8,9] The experiences with flashes in depressive women on SSRIs and the presumed modes of action of this class of antidepressants, have led to several studies evaluating the effects of SSRIs on hot flashes.

Venlafaxine was the first SSRI to be tested on efficacy in the treatment of vasomotor symptoms. Venlafaxine inhibits neuronal serotonin reuptake, but also norepinephrine reuptake, strictly speaking making the drug a selective serotonin-norepinephrine reuptake inhibitor (SNRI) rather than an SSRI. In a pilot evaluation 28 patients took 25 mg venlafaxine daily for 4 weeks.[70] A decrease in hot flash frequency and scores was seen. A subsequent, double-blind study, comparing placebo with three different doses of venlafaxine for 4 weeks, was conducted among 221 women.[58] These women either had a history of breast cancer or were healthy, but reluctant to take estrogens for fear of breast cancer. After randomization and assessment of baseline values, 56 patients received a placebo for 4 weeks, 56 received venlafaxine 37.5 mg, 55 women used 75 mg (37.5 mg for one week and then 75 mg for 3 weeks), and 54 women used 150 mg (37.5 mg for one week, 75 mg for one week and 150 mg for 2 weeks). At the end of the treatment period, a reduction of 27% was seen in hot flash scores in the placebo group, 37% in the group receiving 37.5 mg, 61% in the 75 mg group and also 61% in the 150 mg group. Furthermore, quality of life improved with the use of venlafaxine. However, more side effects, including mouth dryness, decreased appetite, nausea and constipation, were reported in the venlafaxine 150 mg group than in the placebo group. Mouth dryness was the most frequently reported side effect. Nausea was temporary in the majority of the cases and resolved for the greater part with time. Unfortunately, there were no clear data presented concerning the number or percentage of patients

experiencing these side effects. After this double-blind, placebo-controlled trial, an 8-week, open-label continuation-phase study was performed.[71] Of the 221 patients participating in the double-blind study, 102 women completed the open-label phase and were evaluable. The reduction in hot flash scores, as was seen in the double-blind part of the study, was maintained in the patients who were already on active drugs. The women initially on placebo experienced a decrease of about 60% from baseline. Final titrated doses tended to end up closer to 75 mg than to 150 mg per day. Side effects were comparable to those experienced during the randomized trial. Limitations of this study lie in the fact that it was not placebo-controlled nor randomized.

Thus, venlafaxine seems effective for the treatment of hot flashes. Based on the study results, a starting dose of 37.5 mg, to be increased to 75 mg if necessary, seems reasonable. A higher dose (150 mg) does not improve efficacy and has more side effects.

Fluoxetine, another SSRI, was evaluated in a double-blind, randomized, cross-over study.[72] In the trial 72 women participated, who either had a history of breast cancer or were in good health, but reluctant to use hormonal therapy for fear of breast cancer. They received fluoxetine (20 mg/day) or placebo for 4 weeks, followed by a 4-week period of respectively placebo or fluoxetine after crossing over. Fluoxetine was superior to placebo with respect to hot flash scores. A reduction in hot flash scores of 50% was seen in the fluoxetine group and of 36% in the placebo group. With fluoxetine sleeping difficulties improved, but there was a tendency for more mouth dryness. The optimal dose of fluoxetine has not been established in a dose-seeking trial yet.

A pilot trial of the SSRI paroxetine was performed among 30 breast cancer survivors.[73] They received 10 mg paroxetine for one week, followed by 20 mg for 4 weeks. At the end of the study, a reduction in hot flash frequency of 67% was observed. In addition, an improvement in depression, anxiety and quality of life scores was seen. The main side effect was somnolence, which led to dose reduction in two women and discontinuation of the paroxetine in two others. In the following, double-blind study 165 healthy menopausal women were randomized to receive either placebo, 12.5 mg paroxetine controlled release or 25 mg paroxetine controlled release for 6 weeks.[74] The reduction in hot flash scores compared to baseline was 62% in the 12.5 mg paroxetine group, 65% in the 25 mg group and 38% in the placebo group.

A double-blind, cross-over trial with paroxetine was conducted in 152 women, who either had a history of breast cancer or were healthy, but reluctant to use hormonal therapy.[75] These women were randomized to one of four treatment arms: 4 weeks of paroxetine 10 mg or 20 mg, followed by 4 weeks of placebo, or placebo for 4 weeks, followed by paroxetine 10 mg or 20 mg for 4 weeks.

Preliminary results show a decrease of 48% in hot flash scores in the 10 mg paroxetine group and of 58% in the 20 mg paroxetine group, compared to a respectively 13% and 25% reduction in hot flash scores with placebo. Based on these data, paroxetine is as effective as venlafaxine in the treatment of hot flashes.

Summarizing, SSRIs appear to be effective and tolerable for alleviation of vasomotor symptoms in women with a history of breast cancer. Interestingly, none of the studies with SSRIs for alleviating hot flashes mentioned complications from the withdrawal of the medication. There are, however, reports on symptoms arising after SSRI withdrawal in patients treated for depression. These symptoms include anxiety, irritability, dizziness, light-headedness, headache, paraesthesia, insomnia, vivid dreams, fatigue, nausea and low mood.[76-78] Also, no randomized studies have been conducted so far for a period longer than 6 weeks, and therefore, no data are available concerning long-term efficacy.

No studies evaluating the effect of SSRIs on sexuality in women with a history of breast cancer have been done either, although one of the side effects of these drugs is sexual dysfunction.[79,80] Because hot flashes appear to have a negative effect on sexuality as well[29], problems in sexual functioning may well be aggravated with the use of SSRIs.

Furthermore, a recent study by Stearns et al. about the influence of paroxetine on the plasma concentrations of active tamoxifen metabolites in breast cancer patients, puts the use of SSRIs in this group of patients in a somewhat different perspective.[81] Tamoxifen is converted to two active metabolites, endoxifen and 4-hydroxy-tamoxifen, by cytochrome P450 (CYP). SSRIs can inhibit these CYP's. In this study, tamoxifen and its metabolites were measured in the plasma of 12 women who received tamoxifen as adjuvant treatment for their breast cancer. Plasma concentrations were assessed before the start of paroxetine and after 4 weeks. A decrease in endoxifen plasma levels of 64% in women with a wild-type CYP2D6 (a subtype of cytochrome P450) genotype was seen after 4 weeks of paroxetine. In women with a variant CYP2D6 genotype endoxifen concentrations decreased by 24%. Thus, paroxetine, and possibly other SSRIs that interact with CYP2D6, decrease endoxifen concentrations and may negatively influence antiestrogenic activity of tamoxifen in certain breast cancer patients, depending on CYP2D6 genotype.

In a study among 80 newly diagnosed breast cancer patients who were started on tamoxifen as adjuvant therapy, decreased plasma endoxifen concentrations were observed in women with a CYP2D6 homozygous variant or heterozygous genotype compared to women with a homozygous wild-type genotype.[82] In the group of patients carrying a homozygous wild-type genotype, women who were

taking paroxetine (a potent CYP2D6 inhibitor) had a lower mean plasma endoxifen_concentration than women with the same genotype, but not using CYP2D6 inhibitors. In women treated with venlafaxine, a weak inhibitor of CYP2D6, plasma concentrations of endoxifen were slightly reduced as well. Preliminary results from a study in 224 patients receiving tamoxifen as adjuvant treatment for their breast cancer, showed a negative influence on disease-free survival, but not on overall survival, in patients with a CYP2D6 homozygous variant genotype.[83] However, more studies are needed to confirm these results and to evaluate the impact of low endoxifen concentration on tumor suppression in breast cancer patients. Based on these results, no recommendations for or against the concomitant use of tamoxifen and SSRIs can be made yet.

Vitamin E

Anecdotal evidence suggests that vitamin E may be helpful to relieve hot flashes. In the only randomized trial with vitamin E for hot flashes, 104 breast cancer patients received vitamin E (800 IU daily) for 4 weeks, followed by 4 weeks of placebo, or vice versa.[55] Vitamin E was more effective in reducing hot flashes than placebo, but the difference between both was minimal. Patients experienced one hot flash less per day and at the end of the trial they did not prefer vitamin E over placebo. However, vitamin E has no side effects, is inexpensive, widely available, and it allows patients to have at least the placebo effect.

Phytoestrogens

The lower prevalence of hot flashes in Asian women compared to Western women has led to a focus on dietary differences. Eastern women have a high intake of soy products, which contain phytoestrogens in relatively large quantities. Phytoestrogens are plant compounds and can be categorized into two primary classes: isoflavones, the most common form, and lignans. Phytoestrogens have estrogen or antiestrogen effects, depending on many factors, such as ambient estradiol concentration, gender and menopausal status.[59,84,85] Two studies have been conducted to evaluate the potential benefit of phytoestrogens on hot flashes in breast cancer patients. Quella et al. performed a randomized, double-blind, cross-over study among 177 women with a history of breast cancer, of whom two thirds used tamoxifen.[59] They received 4 weeks of soy tablets (150 mg isoflavones per day) or placebo and then crossed over to the opposite arm for another 4 weeks. Phytoestrogens did not reduce hot flashes more than placebo, neither did patients prefer the soy product over placebo.

Another double-blind study showed similar results. After randomization 59 women used a soy beverage containing 90 mg of isoflavones and 64 women a placebo rice beverage for a period of 12 weeks.[86] No difference was seen between the decrease in hot flashes with soy beverage and placebo. Mild gastrointestinal side effects were seen in both groups, but they were worse with the soy drink.
In summary, there is no evidence for a significant beneficial effect on hot flashes by soy products. Moreover, little is known about the safety of the use of phytoestrogens in breast cancer patients.

Black cohosh
Black cohosh (Cimicifuga racemosa) is a herb, traditionally used by Indian Americans for gynaecologic and other conditions.[87] A double-blind study of 85 women with a history of breast cancer, who were randomized to use black cohosh or placebo for 60 days, showed no differences in reduction of hot flashes between both groups.[88] The decrease in the number of hot flashes after 60 days was about 27%.
A recently published pilot study among 21 women using black cohosh for a period of 4 weeks showed a reduction in hot flash scores of 56%.[89] The women included, either had a history of breast cancer, were at risk for developing breast cancer or were in good health, but reluctant to use hormonal therapy for fear of breast cancer. The decrease in hot flash scores seemed to be larger than usually seen with placebo, but the study was not randomized, nor placebo-controlled. Therefore, no conclusions can be drawn about the efficacy of black cohosh for alleviating hot flashes based on this study.
Furthermore, there is no information concerning long-term effects of black cohosh, and no definite data on the safety of this drug in breast cancer patients are available either.

Gabapentin
Gabapentin is a γ-aminobutyric acid analogue. This drug is primarily used as an anticonvulsant, but can also be used for the treatment of neuropathic pain, migraine, essential tremor, panic disorder and social phobia.[57,90] The side effects most frequently seen in studies using gabapentin for the treatment of seizures include somnolence, dizziness, ataxia and fatigue.[91,92]
Recently, gabapentin is evaluated in a randomized, double-blind, placebo-controlled trial in 59 postmenopausal women.[57] After 12 weeks treatment with gabapentin 900 mg per day or placebo, a reduction of 45% in hot flash frequency was seen in the gabapentin group, compared to 29% in the placebo group. Half of the patients receiving gabapentin reported at least one adverse

event, compared to 27% in the placebo group. The most common side effects were somnolence, dizziness and rash with or without peripheral edema. This double-blind study was followed by an open-label treatment, during which the patients could increase the dose of gabapentin to 2300 mg per day, if needed. Of the 54 patients who started the open-label study, 44 wanted to continue treatment with gabapentin for 5 weeks. Of these patients 25% requested a dose of 900 mg or less, 61% a dose between 900 and 1800 mg per day, and 14% a dose between 1800 and 2700 mg per day. An overall reduction of 54% in hot flash frequency was seen compared to baseline. In a pilot study among 22 women with a history of breast cancer and currently on tamoxifen, gabapentin 300 mg was used three times a day for 4 weeks.[93] Of these women 16 completed the study; two did not provide complete data and four withdrew due to side effects, including nausea, rash and excessive sleepiness. A reduction in hot flash frequency of 44.2% and in hot flash severity of 52.6% was observed.
In a placebo-controlled trial, 420 breast cancer patients were randomized to receive placebo, gabapentin 100 mg three times a day (tid) or gabapentin 300 mg tid for 8 weeks.[94] Preliminary results in 324 women show a reduction in hot flash scores from baseline of 18.0% in the placebo group, 30.0% in the gabapentin 100 mg tid and 45.6% in the gabapentin 300 mg tid group. No information regarding side effects has been presented yet.
Gabapentin seems to be effective in the treatment of hot flashes. However, side effects may limit the applicability of gabapentin.

CONCLUSION

Hot flashes are a main symptom associated with menopause. In breast cancer patients hot flashes are frequent and often severe, due to chemotherapy and endocrine treatment. Also, hot flashes appear to impair quality of life in these women, making adequate treatment important.
Several therapeutic options for hot flashes have been studied. Except for progestational agents, none of the therapies described have shown to be as effective in treating hot flashes as estrogen. However, both estrogen and progestagens should be avoided in breast cancer patients, because of the potential risk of tumor recurrence or the development of a new primary breast tumor. There are several alternatives to these hormones, but they are not equally effective and many have side effects. At the moment, clonidine and SSRIs seem to be the best options for treatment of vasomotor symptoms, although no studies addressing the long-term efficacy have been conducted so far. Clonidine reduces hot flashes, and can be used safely in women with a history of breast

cancer. However, it has certain unpleasant side effects and can have a negative influence on other medication. The clinical application of clonidine, therefore, may be restricted due to interaction with concomitantly used medication.
The SSRIs are promising drugs for the treatment of flashes. They appear to be the most effective non-hormonal therapy at the moment. Of the SSRIs venlafaxine is most extensively studied in breast cancer patients, but only data concerning the short-term effects are available. Some side effects are seen with all three SSRIs, but generally they are well tolerated. Although there are no reports so far of SSRI withdrawal symptoms in studies on the treatment of hot flashes, tapering the dose gradually is recommended. In addition, results from studies concerning interaction between tamoxifen and paroxetine, venlafaxine and possibly other SSRIs, should be awaited, as they may influence future recommendations regarding the concurrent use of tamoxifen and SSRIs in certain patients. Nevertheless, based on evidence from literature, venlafaxine is the most effective and best-tolerated non-hormonal drug for the treatment of hot flashes at this moment.

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