Published in final edited form as:
J Natl Compr Canc Netw. 2010 October ; 8(10): 1171–1179.

Nonhormonal Management of Hot Flashes for Women on Risk Reduction Therapy

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Abstract

Hot flashes are very common in women in menopause and can have a detrimental effect on quality of life. Women on risk reduction therapy are particularly prone because treatments, such as tamoxifen, raloxifene, or oophorectomy, have the potential to exacerbate these symptoms. Hormonal treatments, despite the fact that they represent the most effective therapies, are not used for the treatment of hot flashes in these women because of concerns that they may increase the risk for breast cancer. As a result, several nonhormonal therapies have been tested in randomized placebo-controlled trials and shown to be effective, such as paroxetine, venlafaxine, desvenlafaxine, fluoxetine, citalopram, gabapentin, and pregabalin. In addition, several nonpharmacotogic therapies have been tested with various successes. An additional consideration is how some of those drugs, especially fluoxetine and paroxetine, interact with the metabolism of tamoxifen. This article discusses these issues, and provides some recommendations regarding use of nonhormonal therapies for treating hot flashes in women on risk reduction therapy, with an emphasis on pharmacogenomic considerations.

Keywords

Hot flashes; breast cancer; tamoxifen; raloxifene; pharmacogenomics; CYP2D6

Hot Flashes

In the general population, hot flashes occur in 30% to 80% of menopausal women;[1] their frequency, duration, and severity can vary, and significantly interfere with a woman's functional capacity and quality of life.[2] In addition to the bothersome daytime vasomotor symptoms that interfere with activities of daily living, sleep disturbance can be a significant issue, resulting in arousal from sleep and chronic insomnia.[3,4] Hot flashes are believed to be caused by the estrogen withdrawal associated with the perimenopausal and postmenopausal states, likely through secondary effects on thermoregulatory dysfunction.[5]

Both the U.S. Preventive Services Task Force and ASCO currently recommend that chemoprevention for breast cancer risk reduction be discussed and considered as an option for women with increased risk of developing breast cancer.[6,7] For postmenopausal women, the currently approved agents are tamoxifen and raloxifene, both recommended for a maximum of 5 years in women at increased risk of developing breast cancer. For premenopausal women, only tamoxifen is recommended because of the lack of data on raloxifene in this population. Tamoxifen reduces the risk of estrogen receptor (ER)–positive

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breast cancer in women with increased risk by 48%,[8] and raloxifene has shown a similar efficacy with tamoxifen at reducing the risk of invasive breast cancer in the same increased risk population.[9] Given the strong efficacy aromatase inhibitors have shown in the treatment of breast cancer, clinical trials are underway to define their role in its prevention.[10,11] Aromatase inhibitors are not currently recommended for the prevention of breast cancer, although this may change in the future.

A common side effect of tamoxifen, raloxifene, and aromatase inhibitors is the development of hot flashes. Both tamoxifen and raloxifene are selective estrogen receptor modulators (SERMs) and work by interfering with “or modulating” the ER, either in a proestrogenic or an antiestrogenic fashion, depending on the target organ. Thermoregulatory dysfunction is believed to be the mechanism through which SERMs cause hot flashes. Up to 80% of women on tamoxifen experience hot flashes, and 30% of these rate their hot flashes as severe.[12] Although women on raloxifene or aromatase inhibitors experience fewer and less-severe hot flashes than those on tamoxifen, the incidence of hot flashes increases with use of these agents and remains a significant issue.[13,14] Therefore, women undergoing chemoprevention for breast cancer risk reduction experience not only high rates of hot flashes as a result of natural menopause but also a higher rate and severity of hot flashes because of the agents used for chemoprevention. An additional reason for the increased problem with hot flashes in this population is the use of oophorectomy as a risk reduction strategy for some premenopausal women at increased risk, which induces immediate menopause and results in hot flashes in most patients.

Controversies Surrounding Hormone-Based Management of Hot Flashes

By far, the most effective therapy for the treatment of hot flashes is estrogen therapy. Estrogen therapy reduces the frequency of hot flashes in symptomatic women by 77% and also significantly reduces the severity.[15] Different formulations of estrogen seem to be equally effective in hot flash management.[16] However, results from the Women’s Health Initiative (WHI) trial found 26% increase in breast cancer incidence among healthy women on hormone (estrogen and progesterone) therapy.[17] In addition, women with a history of breast cancer in the HABITS study were found to have an increased risk of breast cancer recurrence if they were prescribed hormone therapy (22% vs. 8% at 5 years).[18] However, no difference was seen in mortality in the HABITS trial, and a very similar study, the Stockholm trial, did not find an increased incidence of breast cancer with the use of hormonal therapy.[19] In addition, although the hormone therapy used in these studies was long-term, short-term low-dose estrogen has also been found to effectively reduce hot flashes.[20] Overall, it is currently accepted that if estrogen therapy is used for the management of hot flashes, this should be done for the shortest effective period.[1]

Progesterone therapy alone is also very effective for the management of hot flashes. Oral megestrol acetate has been found to reduce hot flashes in 75% to 80% of patients, and similar results have been found with the use of intramuscular, long-acting depomedroxyprogesterone (DMPA).[21-23] However, given the lack of definite data on the safety of progesterone agents in relation to breast cancer risk, no safe conclusions can be drawn regarding their use for the primary treatment of hot flashes in women at increased risk for breast cancer.[24]

Nonhormonal Pharmacologic Management of Hot Flashes

Given the above controversies surrounding estrogen-and progesterone-based therapies for the treatment of hot flashes, significant progress has been made regarding the use of nonhormonal-based therapies, which theoretically should not increase the risk of breast cancer. Among the nonhormonal therapies, the selective serotonin reuptake inhibitors

(SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and the anticonvulsant medications gabapentin and pregabalin, are the most studied and effective (Table 1). Centrally acting compounds, such as clonidine and methyldopa, have a high risk for side effects and are currently not recommended. Finally, several complementary and alternative compounds and behavioral therapies might eventually be shown to have a role in hot flash management (Table 1).

Venlafaxine

Two randomized, placebo-controlled trials have shown efficacy in reducing hot flashes.[25,26] The first study randomized 190 patients to either placebo or oral venlafaxine, 37.5, 75, or 150 mg/d.[25] All patients were started at a dose of 37.5 mg/d and the dose was increased to target in the 75 and 150 mg/d groups. After 4 weeks, hot flashes were reduced by 27%, 37%, 61%, and 61%, respectively. The 150 mg dose was found to be associated with significantly more side effects, such as dry mouth, nausea, and constipation. The second trial randomized 80 patients to 75 mg venlafaxine extended-release or placebo for 12 weeks (with a 37.5 mg/d dose used in the first week) and concluded that venlafaxine was beneficial,[26] Finally, in another trial, 109 women were randomized between a single DMPA intramuscular injection and 75 mg/d venlafaxine for 6 weeks.[27] Venlafaxine decreased hot flashes by 55%, whereas DMPA injections decreased them by 79%. The respective effects are similar to results from prior studies discussed earlier.[23,25] Venlafaxine, 75 mg/d, seems to balance efficacy with side effects best and is the currently recommended dose, with a starting dose of 37.5 mg/d for 1 week.

Desvenlafaxine

Desvenlafaxine, the succinate salt form of the major active metabolite of venlafaxine, has been tested in 2 randomized controlled studies in women with hot flashes.[28,29] In a 5-arm study, 707 women were randomized to either placebo or desvenlafaxine, 50, 100, 150, or 200 mg/d. Hot flashes were reduced by 51%, 55%, 64%, 60%, and 60%, respectively, with toxicities including dry mouth, nausea, insomnia, and somnolence, which were dose-dependent.[28] In the other study, 567 women were randomized to placebo, 100 or 150 mg/d. After 12 weeks, reductions were seen in hot flashes of 47%, 60%, and 66% respectively. Desvenlafaxine is, therefore, an effective treatment for hot flashes and the dose of 100 mg/d is recommended, with a starting dose of 50 mg/d for 3 days.

Paroxetine

Two randomized placebo-controlled trials in women with hot flashes have been performed with the SSRI paroxetine.[30,31] The first trial randomized 156 women to placebo or paroxetine, 12.5 or 25 mg/d. After 6 weeks, hot flashes were reduced by 38%, 62%, and 65%, respectively.[30] Headache, nausea, and insomnia were the most frequent side effects. The second trial randomized 151 women to either placebo or paroxetine, 10 or 20 mg/d.[31] After 4 weeks, reductions in hot flashes were seen in 14%, 41%, and 52% of women, respectively, with the difference between the 10 and 20 mg dose being not statistically significant. The starting recommended dose for paroxetine is 10 mg/d, because it seems to be as effective and better tolerated than higher doses. An increase to 20 mg/d can be considered. Paroxetine, being a potent inhibitor of CYP2D6, should not be used in women with tamoxifen, as will be discussed later.

Fluoxetine

Two randomized controlled studies of fluoxetine versus placebo have been conducted.[32,33] The first study randomized 81 women to placebo versus fluoxetine, 20 mg/d.[32] After 4 weeks, hot flashes were reduced by 36% and 50%, respectively. Side effects included

nausea, fatigue, insomnia, nervousness, and, constipation. The other study randomized 150 women to placebo, 20 mg of fluoxetine, or 20 mg of citalopram. Although no differences were observed among the arms, baseline measurements of hot flashes were collected on the first day of treatment rather than before initiation of treatment, which may have artificially reduced the baseline incidence of hot flashes, because antidepressants can have an immediate effect in decreasing hot flashes. In fact, venlafaxine is known to reduce hot flashes by 31% on the first day of treatment.[34] Generally, given the efficacy of several other antidepressants against hot flashes, fluoxetine is not used as frequently as other agents in clinical practice. In addition, fluoxetine, like paroxetine, is a potent inhibitor of CYP2D6 and should also not be used with tamoxifen.

Citalopram

The stronger evidence for citalopram comes from a randomized controlled study of 254 patients randomized to placebo or citalopram, 10, 20, or 30 mg/d.[35] At the end of the study, hot flashes were reduced by 20%, 46%, 43%, and 50%, respectively. Side effects were minimal. In addition, a pilot trial of 22 women who experienced inadequate relief from venlafaxine showed a 53% reduction in hot flashes after treatment with citalopram, although randomized studies are needed to confirm this observation.[36] Therefore, citalopram is a reasonable alternative when other antidepressants are not effective or desired. Citalopram, when used, is recommended at a dose of 10 to 20 mg/d.

Gabapentin

Three randomized placebo-controlled studies have compared gabapentin with placebo for the treatment of hot flashes.[37,38] The first study randomized 59 women to placebo or gabapentin, 900 mg/d.[37] At 12 weeks, hot flashes were reduced by 29% and 45%, respectively. After 12 weeks, in an open-label study, patients with an increased dose of 2700 mg/d experienced a 54% reduction in hot flashes without an apparent increase in side effects.[37] In the other trial, 420 patients with breast cancer and hot flashes were randomized to placebo or gabapentin, 300 or 900 mg.[38] At 4 weeks, hot flashes were reduced by 21%, 33%, and 49%, respectively. A third trial randomized 50 women to either placebo, 0.625 mg of conjugated estrogen, or 2400 mg of gabapentin for 12 weeks.[39] Hot flashes were reduced by 54%, 72%, and 71%, respectively.

Gabapentin has also been studied in patients for whom other therapies failed for treating hot flashes. In a study of 91 patients who experienced an inadequate response to antidepressant treatment of hot flashes and were subsequently treated with gabapentin, results showed a 50% reduction in hot flashes.[40] In general, gabapentin is effective in managing hot flashes in patients with breast cancer, as suggested by a pooled analysis of the available studies.[34] It is recommended at a dose of 900 mg/d in 3 divided doses, with a starting dose of 300 mg/d.

Pregabalin

Pregabalin, a newer-generation antidepressant similar to gabapentin, was tested in a randomized placebo-controlled study of 163 women randomized to either placebo or pregabalin, 75 mg twice daily or 150 mg twice daily for 6 weeks.[41] Hot flashes were reduced by 50%, 65%, and 71%, reppectively. Side effects included insomnia, dizziness, weight gain at both doses of pregabalin, and cognitive dysfunction at the 150-mg dose. As a result, the recommended target dose is 75 mg twice daily, with a starting dose of 50 mg/d.

Other Centrally Acting Compounds

Bellergal, clonidine, methyldopa, and veralipride are other centrally acting compounds that have been tested for the treatment of hot flashes in several clinical trials.[42-45] Although they

all have shown a moderate, or inconsistent, effect in reducing hot flashes, they are associated with significant side effects, such as nausea, fatigue, mouth dryness, constipation, drowsiness, and insomnia. These compounds are not recommended for managing hot flashes.

Complementary and Alternative Agents

Isoflavone-phytoestrogens are naturally occurring compounds found primarily in soy products that have both estrogenic and antiestrogenic activity.[46] Several clinical trials have failed to show any benefit associated with an isoflavone-rich soy protein diet or dietary supplements derived from red clover, which is another source of isoflavones.[43] Lignan, another source of phytoestrogens found primarily in whole grains, vegetables, and flaxseed, have structural similarities with estradiol and tamoxifen. A double-blinded placebo-controlled trial of 87 women who were randomized to muffins with 25 g of flaxseed, 25 g of soy, or wheat showed that after 16 weeks only flaxseed muffins reduced the frequency of hot flashes.[47] Another placebo-controlled North Central Cancer Treatment Group (NCCTG) trial of flaxseed versus placebo has completed accrual, and results should be reported in the near future.

Although an initial meta-analysis of 4 trials from the 1980s suggested that black cohosh had a beneficial effect on hot flashes,[48] more recent placebo-controlled clinical trials have failed to confirm that observation.[49,50] Given concerns about adverse effects of black cohosh on the liver and its lack of proven efficacy, it is currently not recommended for managing hot flashes.

In another study comparing placebo and vitamin E, 800 IU/d, among 120 women,[51] the effect of vitamin E was minimal at best. Concerns regarding the safety of vitamin E seem to be unfounded based on a recent meta-analysis showing no increase in cancer risk.[52] Vitamin E can be considered for treatment of mild hot flashes at a dose of 400 IU twice daily, given that it may relieve hot flashes a little more than a placebo, it is inexpensive, and it is safe.

Randomized controlled trials of several other herbal remedies, such as evening primrose oil, dong quai, ginseng, and wild yam, have failed to show a beneficial effect. Dehydroepiandrosterone (DHEA) has been tested in pilot studies, but placebo-controlled studies have not been reported.

Nonpharmacologic Management of Hot Flashes

Several nonpharmacologic therapies have been investigated for possible beneficial effects against hot flashes. Acupuncture has been used for thousands of years and has been found to be safe and effective for treating chronic pain and chemotherapy-induced nausea and vomiting. Several pilot studies and randomized trials have evaluated the role of acupuncture for hot flashes, but a recent meta-analysis of 11 randomized trials found no evidence supporting its use.[53] Issues regarding the need for practitioner’s experience and the lack of a proper placebo (even sham procedures, used in many trials, can have a physiologic effect) make conclusions from these trials difficult. Nevertheless, acupuncture is not recommended for treating hot flashes at this time.

Yoga has been tested for the control of hot flashes, and several trials have suggested an improvement in vasomotor symptoms when women practice yoga. However, whether yoga is better than placebo is unclear, and a recent review of the literature has suggested that the use of yoga is not supported by the current evidence.[54] Regarding exercise, 2 small prospective randomized trials from Sweden randomized women with hot flashes to a 12-week exercise schedule versus estrogen[55] or observation.[56] A moderate reduction in hot

flashes was seen compared with placebo, but estrogen therapy was clearly superior. A larger study, however, showed that moderate to intense exercise in postmenopausal, sedentary, obese women increased the rate of hot flashes.[57] As a result, whether exercise leads to a reduction in hot flashes in unclear; more research is underway.

Relaxation training and paced breathing have been tested in several small trials. A recent review of the literature found that most studies using relaxation as an intervention showed positive results.[58] However, most studies have small sample sizes and the relaxation techniques vary, making interpretation difficult. Although hypnosis has been found to be useful in the management of multiple medical conditions, such as pain, anxiety, and insomnia, and has been found to reduce anxiety and distress in breast cancer patients, only pilot studies have been performed in the setting of hot flashes. Although the results appear promising, with a 68% reduction in the treatment group in a study of 51 patients with breast cancer, larger randomized trials are needed and are underway.[59]

Stellate ganglion block is a technique in which an anesthetic is injected at the level of the C6 vertebra to block the sympathetic chain at that level.[60] Although the technique is primarily used to control pain syndromes and vascular insufficiency syndromes, several pilot studies found a benefit in the treatment of hot flashes, and larger randomized studies are underway. Finally, for mild hot flashes, interventions can be suggested, such as the use of a fan, loose-fitting clothing, cold drinks, lower room temperature, and dietary modifications, such as avoidance of alcohol and spicy foods.[5]

Tamoxifen Pharmacogenomics

Increasing evidence suggests that the pharmacogenomics of tamoxifen are an important consideration when given to women with breast cancer. Tamoxifen is a prodrug with weak antiestrogenic activity, which is metabolized primarily by the hepatic enzyme CYP2D6 into several metabolites.[61,62] The most abundant active metabolite is endoxifen.[61,63] Depending on ethnicity, approximately 5% to 10% of women are poor metabolizers of CYP2D6 and have lower endoxifen levels.[62,64,65] Several prospective and retrospective observational studies have found that poor metabolizer status is associated with a 2- to 4-fold increase in risk for breast cancer recurrence.[66-68] Interestingly, women who are poor metabolizers experience fewer hot flashes than those who are extensive metabolizers,[69] and at least one retrospective study found that women on tamoxifen who do not experience hot flashes had a higher chance of breast cancer recurrence.[70] However, several other retrospective observational studies found no association between poor metabolizer status and risk of breast cancer recurrence, and therefore this remains controversial.[71-73] Nevertheless, CYP2D6 testing is increasingly being performed by oncologists around the country and influencing decision-making, mainly for postmenopausal patients with breast cancer. In fact, the above evidence has led the FDA to issue a black box warning regarding the use of tamoxifen in postmenopausal breast cancer patients who are poor metabolizers of CYP2D6 because of genotype or drug interaction.[74]

Although CYP2D6 testing is being considered for patients with breast cancer when tamoxifen is contemplated, it is currently not recommended in other clinical settings, such as for women with ductal carcinoma in situ (DCIS) or those who consider tamoxifen a risk reduction strategy. The main reason for the lack of recommendations is the absence of evidence showing that women who are poor metabolizers of CYP2D6 do not benefit from tamoxifen in these settings. When no alternative option exists, such as the treatment of DCIS or risk reduction pharmacotherapy in premenopausal women, in whom only tamoxifen is approved, not testing for CYP2D6 is an easier choice. However, in the case of risk reduction pharmacotherapy in postmenopausal women, both tamoxifen and raloxifene are approved.

Theoretically, knowledge of the CYP2D6 status could be used in this setting to preferentially choose raloxifene over tamoxifen for women who are poor metabolizers and are otherwise considering treatment with tamoxifen. As a result, if the choice between tamoxifen over raloxifene is being contemplated for postmenopausal women at high risk for breast cancer, the issues pertaining to CYP2D6 metabolism of tamoxifen should be brought to the patient's attention and considered. CYP2D6 is not involved in the metabolism of raloxifene or the aromatase inhibitors, and therefore metabolizer status has no influence on the efficacy of these drugs.

Medications for Hot Flashes That Might Inhibit Tamoxifen Metabolism

Several medications are strong inhibitors of CYP2D6, and some have been shown to interfere with tamoxifen metabolism (Table 2). From the medications discussed thus far, fluoxetine and paroxetine are both potent inhibitors of CYP2D6 and significantly reduce endoxifen levels in tamoxifen-treated women.[65] Fluoxetine and paroxetine can convert a person who is an extensive CYP2D6 metabolizer to poor CYP2D6 metabolizer. Citalopram is a weaker inhibitor of CYP2D6 and has not been shown to phenoconvert individuals who are extensive metabolizers into poor metabolizers, although some reduction in endoxifen levels may be seen.[65] The significance of this possible reduction in endoxifen levels is unclear. Venlafaxine and desvenlafaxine are very weak inhibitors of CYP2D6. Specifically, venlafaxine has been shown to have no effect on endoxifen levels in tamoxifen-treated women, as expected from its lack of significant inhibitory potential.[65] Finally, gabapentin and pregabalin are not known to inhibit CYP2D6 or any other hepatic enzyme. Recent reviews have addressed the CYP2D6 inhibitory potential of various medications and have provided clinical recommendations.[75,76]

Recommendations for Nonhormonal Pharmacologic Management of Hot Flashes in Women on Risk Reduction Therapy

The authors recommend that all patients with hot flashes be educated on behavioral modification techniques, such as sipping cold drinks, lowering the room temperature, wearing loosely fitted clothing, and avoiding alcohol and spices in the diet. For mild hot flashes, 400 IU of vitamin E twice daily can be attempted. For women with breast cancer undergoing risk reduction therapy who experience moderate to severe hot flashes, pharmacologic therapy is indicated. Recommended options for treatment are outlined in Table 1. Although little work has been done comparing nonhormonal regimens to each other, a recent trial addressed this issue. This study, involving 66 patients, compared gabapentin with venlafaxine.[77] Patients were treated for 4 weeks with either gabapentin or venlafaxine and then switched over, after a washout period. Patient preference was the primary outcome. Although both drugs reduced hot flashes by 66%, at the end of the crossover study more patients preferred to stay on venlafaxine than gabapentin (68% vs. 32%).

If tamoxifen is being used, then fluoxetine and paroxetine should be avoided in favor of other pharmacotherapies. In fact, women who are on tamoxifen and potent inhibitors of CYP2D6 should substitute these inhibiting medications with other options, if possible. Several other potent CYP2D6 inhibitors are not used for the treatment of hot flashes but also should be avoided if possible in tamoxifen-treated women. These medications (bupropion, duloxetine, thioridazine, perphenazine, pimozide, quinidine, ticlopidine, terbinafine, and cinacalcet) were recently reviewed.[76] Modest reductions in endoxifen levels are of unclear significance, and therefore no specific recommendations exist against the use of citalopram. Venlafaxine, desvenlafaxine, gabapentin, and pregabalin are not CYP2D6 inhibitors and have no contraindications to their coadministration with tamoxifen.

Conclusions

Several effective pharmacologic nonhormonal therapies exist for women with hot flashes. Fluoxetine and paroxetine specifically are potent inhibitors of CYP2D6, the main enzyme responsible for the metabolism of tamoxifen. As a result, women on risk reduction therapy who are treated with tamoxifen should avoid using these medications in favor of other options. CYP2D6 inhibition has no effect on other risk reduction strategies, such as raloxifene or oophorectomy.

Acknowledgments

Dr. Sideras has disclosed that he has no financial interests, arrangements, or affiliations with the manufacturers of any products discussed in the article or their competitors. Dr. Loprinzi had disclosed that he has received research funding from the North Central Cancer Treatment Group.

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Table 1

Nonhormonal Treatments of Hot Flashes Discussed

Nonhormonal Management	Best Evidence	Effect	Recommendation
Venlafaxine	Randomized placebo-controlled trials	Positive	Recommended
Desvenlafaxine	Randomized placebo-controlled trials	Positive	Recommended
Paroxetine	Randomized placebo-controlled trials	Positive	Recommended (should not be used with tamoxifen)
Fluoxetine	Randomized placebo-controlled trials	Positive	Recommended (should not be used with tamoxifen)
Citalopram	Randomized placebo-controlled trials	Positive	Recommended
Gabapentin	Randomized placebo-controlled trials	Positive	Recommended
Pregabalin	Randomized placebo-controlled trials	Positive	Recommended
Other Centrally Acting:			
Bellergal	Randomized placebo-controlled trials	Moderate effect, inconsistent results, too many side effects	Not recommended
Clonidine			
Methyldopa			
Veralipride			
Isoflavone phytoestrogens	Randomized placebo-controlled trials	No effect	Not recommended
Lignan phytoestrogens	Randomized placebo-controlled trials	Possible effect	More evidence needed
Black cohosh	Randomized placebo-controlled trials	Inconsistent effect, possible harm	Not recommended
Vitamin E	Randomized placebo-controlled trials	Mild effect	Recommended
Herbal Remedies			
Evening primrose oil	Randomized placebo-controlled trials	No effect	Not recommended
Dong quai			
Ginseng			
Wild yam			
Dehydroepiandrosterone (DHEA)	Pilot studies		More evidence needed
Acupuncture	Randomized placebo-controlled trials	Inconsistent effect	Not recommended
Yoga	Randomized controlled trials	Not clear if better than placebo effect	Not recommended
Exercise	Randomized controlled trials	lnconsistent effect	More evidence needed
Relaxation training	Pilot, heterogeneous studies	Positive	More evidence needed
Hypnosis	Pilot studies	Positive	More evidence needed
Stellate ganglion block	Pilot studies	Positive	More evidence needed

Table 2

Inhibitory Potential of Medications Used for the Treatment of Hot Flashes

Medication	CYP2D6 Inhibitory Potential	Likely Effect on Tamoxifen Metabolism
Paroxetine	Potent inhibitor	Complete inhibition
Fluoxetine	Potent inhibitor	Complete inhibition
Citalopram	Moderate inhibitor	Minimal effect
Venlafaxine	Weak inhibitor	No effect
Desvenlafaxine	Weak inhibitor	No effect
Gabapentin	No inhibitor	No effect
Pregabalin	No inhibitor	No effect