



Management of vasomotor symptoms in cancer patients

Ling Zhu^{1,2,*} , Tammy T. Hsieh³, Tara K. Iyer⁴, Alicia K. Morgans⁵, Ole-Petter R. Hamnvik² 

¹Department of Endocrinology, Singapore General Hospital, Singapore 169856

²Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115, United States

³Division of Aging, Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115, United States

⁴Menopause and Midlife Clinic, Division of Women's Health, Department of Medicine, Brigham and Women's Hospital, Boston, MA 02215, United States

⁵Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, United States

*Corresponding author: Ling Zhu, Department of Endocrinology, Singapore General Hospital, 20 College Road, Singapore 169856 (gmszlin@nus.edu.sg).

Abstract

Many cancer treatments can lead to reduced levels of sex hormones, which in turn may cause vasomotor symptoms (VMS) such as hot flashes. These symptoms are associated with impaired quality of life, as well as suboptimal tolerability of and adherence to cancer treatment. Hormone therapy, performed by increasing estradiol or testosterone levels, is the gold standard for treatment of VMS. However, this approach is generally contraindicated in patients with hormone-sensitive cancers. Nonhormone agents with low to moderate efficacy in controlling VMS are available, but their use may be limited by side effects and tolerability. In this narrative review, the approach to VMS in cancer patients will be discussed. The evidence for various treatment options, including novel agents such as fezolinetant that target the hypothalamic thermoregulatory pathway, will be evaluated. Finally, special considerations in different patient populations based on cancer types (eg, breast, prostate) and age groups (eg, older adults) will be explored.

Key words: hot flashes; menopause; breast cancer; prostate cancer; cancer survivors.

Implications for Practice

Optimal management in cancer survivorship requires timely identification and management of symptoms. Hormone therapy is the gold standard treatment for VMS but is contraindicated in hormone-sensitive cancers. There is growing evidence demonstrating the efficacy of nonhormone options. While generally well tolerated by many, these agents can be associated with side effects that cancer patients may be particularly susceptible to. Encouragingly, emerging drug targets have enabled the development of novel pharmacologic treatments, thereby expanding treatment options for cancer patients with VMS. A comprehensive understanding of these therapeutic agents would enable health care providers to plan effective treatment strategies for cancer survivors experiencing VMS.

Introduction

An increasing number of people are living with a diagnosis of cancer, due to earlier diagnosis and improved survival of many cancer types.¹ In many cases, this means that patients are receiving cancer treatments for longer, or living with long-term side effects of cancer treatments. As a result, there is a growing focus on management of side effects of cancer treatment. One common consequence of many cancer treatments is hypogonadism, marked by a reduced level of sex hormones such as testosterone and estradiol. This can occur as a primary treatment goal in the setting of hormone-responsive cancers, as a side effect during gonadotoxic chemotherapy, or as a result of the underlying cancer itself.^{2,3} Hypogonadism is frequently associated with vasomotor symptoms (VMSs), such as hot flashes. Traditionally, VMSs are regarded as hallmark symptoms of menopause in women entering the end of reproductive years.⁴ In the general population, up to 79% of menopausal women and 33% of aging men are affected by

VMS.^{5,6} In menopausal women, VMS have a median duration of 7 years, or even longer in those with early onset of VMS, and/or African American race.⁷

The management of VMS is an area of unmet needs in cancer survivorship, and the magnitude of the symptom burden is not to be underestimated.⁸ Globally, breast and prostate cancers, both of which are frequently hormone-sensitive, are amongst the most common cancers. Collectively, they account for 19% of all cancer diagnoses.⁹ The incidence of VMS is particularly high in breast cancer patients on endocrine therapy, including ovarian suppression or ablation, tamoxifen, and aromatase inhibitors (AIs), with a rate of up to 93% of patients depending on treatment type.^{10–12} Anticancer treatment interruption and discontinuation rates for breast cancer patients have been reported to be greater than 20%.^{13,14} The key contributing factor to such poor adherence has been consistently cited as treatment side effects such as VMS.^{15,16} VMSs have also been widely reported in prostate cancer patients on

Received: 20 July 2024; Accepted: 11 November 2024.

© The Author(s) 2025. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

androgen deprivation therapy (ADT).¹⁷ Unfortunately, the majority of cancer patients with VMS do not receive timely and effective intervention.⁸ Furthermore, hormone therapy (HT), the gold standard treatment for VMS, is often contraindicated in patients with hormone-sensitive cancers.⁴ Prompt recognition and appropriate management of VMS in such patients are integral components of holistic and effective cancer care.

We recognize that hormone-based therapies are used in many different settings in management of cancer and cancer survivorship. For the purpose of this review, terminology will be standardized according to [Table 1](#).

Pathophysiology of VMS in cancer patients

Following an abrupt decline in estradiol level in endocrine therapy-treated cancer patients and postmenopausal women, the development of VMS is largely orchestrated by changes in thermoregulatory neurons and the downstream responses.¹⁸ In prostate cancer patients treated with ADT, suppression of luteinizing hormone (LH) causes decline in testosterone to castrate levels.¹⁹ As 85% of circulating estradiol in men is derived from peripheral aromatization of testosterone, a decline in testosterone level corresponds to a fall in estradiol.²⁰ This process results in a hormonal milieu similar to that in postmenopausal women or women undergoing endocrine therapy. The subsequent steps leading to VMS, however, are not well-established.^{21,22}

In healthy individuals, core body temperature range is regulated by physiological and behavioral mechanisms, aimed to achieve a target that would enable smooth performance of body functions.²³ In individuals with VMS, such homeostasis is altered. This leads to marked narrowing of the thermoneutral zone (defined as the range of temperatures between core thresholds for thermogenesis and thermal dissipation)²⁴ and premature triggering of thermoregulatory response, resulting in significant VMS at temperatures well tolerated by others.²⁵

Following the elucidation of the hypothalamic thermoregulatory pathway, understanding of the pathophysiology of VMS has further expanded. A drop in sex hormone levels leads to an increased expression of kisspeptin by the Kisspeptin/Neurokinin B/Dynorphin A (KNDy) neurons in the arcuate nucleus of hypothalamus.^{26,27} This activates the hypothalamic-pituitary-gonadal axis with increased generation of gonadotropin-releasing hormone (GnRH) pulses in hypothalamic neurons and an increase in secretion of LH. Additionally, the KNDy neurons release neurokinin B (NKB). NKB acts on the neurokinin 3 receptor (NK3R) and activates the thermoregulatory center in the median preoptic nucleus, triggering heat dissipation, vasodilation, and sweating that characterize VMS ([Figure 1](#)).²⁸

Clinical assessment of a patient presenting with VMS

A patient with cancer may experience VMS either as result of hypogonadism from endocrine therapy, cytotoxic chemotherapy, surgery or pelvic irradiation; or due to physiological reproductive aging and menopausal transition. The onset of VMS can be accelerated by cancer or cancer treatment. The menopausal transition period is extremely variable in terms of age of onset, duration, and presentation.²⁹ Patients' perception of the symptoms can also be influenced by culture, further increasing the complexity of the assessment.³⁰ Thorough history and physical examination are therefore essential when approaching a patient presenting with VMS.

Typically, hot flashes are described as episodes of sudden sensation of extreme heat, originating from the upper chest and face, spreading to the rest of the body and lasting 2-4 minutes. These may be followed by profuse sweating and can also be accompanied by palpitations and anxiety.⁴ As the body temperature drops due to sweating, shivering can ensue. Hot flashes occur more often in the afternoon and night, with varying frequencies ranging from every few days to every hour.^{31,32} Bothersome nocturnal hot flashes and sweating can lead to significant sleep disturbance.^{33,34}

While the cause of VMS can be seemingly apparent in a patient receiving cancer treatment with the foreseeable side effects, it is important for clinicians to be mindful of the differential diagnoses that may exist ([Table 2](#)).³⁵ Fortunately, many of these conditions can be excluded based on history and clinical findings. Among the medical conditions that can cause flashing, discriminating clinical features include onset, duration, associated symptoms, and triggers. Of note, hot flashes that occur with menopause or hypogonadism in cancer patients can present as “wet” flashes (ie, associated with sweating), while flashings mediated by vasoactive substances occur as a result of smooth muscle dilatation and are typically “dry” flashes (ie, not associated with sweating).³⁶

Determination of severity of hot flashes is another key step in clinical assessment. There is no standardized method of defining severity in the clinical setting. Measurement tools, such as the Kupperman Menopausal Index, the Greene Climacteric Scale, and the Menopausal Rating Scale, have been developed to quantify the severity of climacteric symptoms.³⁷⁻⁴¹ These tools encompass a broad range of menopausal symptoms and rely largely on patients' self-reporting. Specific to hot flashes, options include the 7-day Daily Hot Flash Diary that uses a 4-category severity scale (mild, moderate, severe, and very severe) and the Hot Flash Related Daily Interference Scale, both of which have been used in the research of VMS in patients with cancer.⁴²⁻⁴⁴ A different standard is used for drug approval in the pharmaceutical industry—the Food and

Table 1. Terminology and description of hormone-related treatments used in the present review.

Terminology	Description
Hormone therapy	Drugs which aim to increase levels of estradiol or testosterone, including: <ul style="list-style-type: none"> • Estrogen or combined estrogen and progestogen therapy in women for management of symptoms of menopause, also known as menopausal hormone therapy. • Testosterone therapy in men with hypogonadism.
Endocrine therapy	Drugs which alter the levels of, or block the effects of hormones in the treatment of hormone-sensitive cancers, including: <ul style="list-style-type: none"> • Ovarian suppression, tamoxifen, and aromatase inhibitors in breast cancer treatment. • Androgen deprivation therapy in prostate cancer treatment.

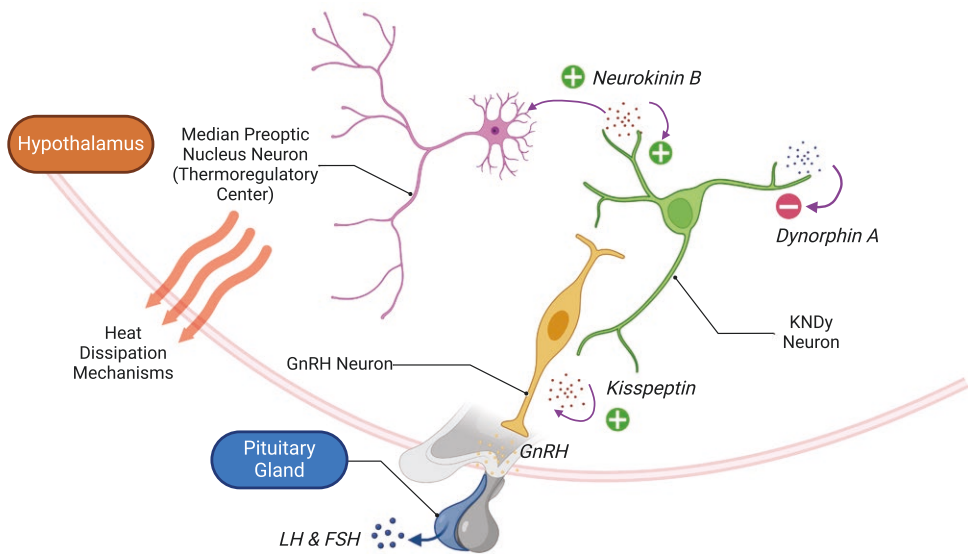


Figure 1. Diagram illustrating the role of the KNDy neuron and its associated signaling pathway in generation of vasomotor symptoms. KNDy neuron is activated by NKB and inhibited by the endogenous opioid peptide dynorphin A. Following menopause, hypertrophy of KNDy neurons leads to increased kisspeptin release, and in turn GnRH secretion and LH pulses. In addition, NKB release is increased, which further stimulates kisspeptin release. NKB also acts on NK3R in the thermoregulatory center to trigger heat dissipation responses, leading to vasomotor symptoms. Abbreviations: FSH, follicle stimulating hormone; GnRH, gonadotropin-releasing hormone; KNDy, Kisspeptin/Neurokinin B/Dynorphin A; LH, luteinizing hormone; NK3R, neurokinin 3 receptor; NKB, neurokinin B.

Table 2. Causes of flashing and sweating disorders.

Endocrinologic conditions	Drugs
Thyrotoxicosis	Vasodilators (eg, nitrates)
Hypoglycemia	Calcium channel blockers
Hypogonadism	Nicotinic acid
Cushing syndrome	Opiates
	Cholinergic drugs
Neoplasms	Bromocriptine
Medullary thyroid cancer	Cyproterone acetate
Renal cell carcinoma	Cyclosporine
Pancreatic neuroendocrine tumor	Rifampin
Pheochromocytoma	Sildenafil
Carcinoid syndrome	Tamoxifen
	Raloxifene
	Aromatase inhibitors
	GnRH agonists/antagonists
	Androgen receptor signaling inhibitors
	Foods
Neurologic conditions	Caffeine
Anxiety	Spicy food
Migraine	Alcohol
Dysautonomia	Monosodium glutamate
	Sodium nitrite
Systemic Conditions	
Systemic mastocytosis	Cardiovascular conditions
Polycythemia	Mitral valve disease
Sepsis	

Drug Administration (FDA) defines severity of VMS as mild (sensation of heat without sweating), moderate (sensation of heat with sweating, able to continue activity), and severe

(sensation of heat with sweating, causing cessation of activity).⁴⁵ This stratification of severity is relatively simple and probably the most practical in the real-world setting.

Decision-making in management of VMS in cancer patients

Comprehensive guidelines have been developed to guide the management of menopausal symptoms such as VMS.^{4,46,47} These generally recommend HT as first-line therapy due to superior efficacy and tolerability as compared with non-hormone options. However, decision-making may be more complex in cancer patients. In many cases, HT is avoided due to concern for recurrence or growth of hormone-sensitive cancers or risk of venous thromboembolism.⁴⁸ In the subsequent sections, efficacy and safety of hormone- and nonhormone-based management options in cancer patients will be discussed.

Nonpharmacological management

Lifestyle interventions, such as behavioral adaptations, can be easy to execute and may be considered in those with mild symptoms. These include turning down the thermostat, keeping surroundings cool, using fans or cooling devices, wearing clothing in layers to enable easy adjustment as required, and avoidance of triggers such as spicy food and alcohol.^{49,50} The use of these behavioral strategies is likely widespread, but due to a lack of robust evidence supporting their use, they are not currently recommended as standard management of VMS.⁴⁶

Many observational and interventional studies have explored nonpharmacological strategies for managing VMS. While some studies reported positive outcomes, interpretation and application of the results can be challenging due to heterogeneity in study design, intervention types, patient populations, and outcome measures. Consequently, there is a lack of robust data supporting the dose-response relationship.⁴⁶

Additionally, the short study durations often hinder our understanding of the sustainability of these effects. A summary of the existing evidence and guideline recommendations on a variety of nonpharmacological interventions is listed in [Table 3](#). As a start, promotion of healthy lifestyle forms part of cancer survivorship care and can be initiated in most health care institutions. As menopause transition is a risk factor for cardiovascular disease,¹¹¹ optimization of metabolic health should be recommended to patients as part of holistic cancer management. The efficacy of weight loss and exercise in reduction of VMS, however, has yet been firmly established, hence these strategies should not be promoted primarily as VMS therapy. Cognitive-behavioral therapy, clinical hypnosis, and stellate ganglion block, though shown to have some beneficial effects, require trained personnel and may not be readily accessible to all patients. The evidence for other interventions such as acupuncture, soy food, and black cohosh, is currently insufficient for them to be universally endorsed by major guidelines.⁴⁶ Given the multiple barriers to incorporating research finding into clinical practice, open discussions should be conducted between the clinicians and patients when making treatment decisions.

Pharmacological management

Hormone therapy

Currently, HT is the gold standard for management of VMS in postmenopausal women, provided its use is not contraindicated (eg, in patients with certain cancer types).⁴ When compared with placebo, oral HT has been shown to lead to 75% reduction in the frequency of hot flashes.¹¹² In women with previous hysterectomy, an estrogen-only preparation is the HT of choice. In women with an intact uterus, a progestogen is prescribed with estrogen to reduce the risk of endometrial hyperplasia.⁴⁷ The benefits of HT extend beyond its efficacy in improving VMS, particularly in younger women with surgical menopause. For instance, it has been shown to effectively reduce genitourinary symptoms and prevent fractures.⁴

The concern with using HT arose following the early findings of the Women's Health Initiative (WHI), which evaluated the benefits and risks of conjugated equine estrogens combined with medroxyprogesterone acetate (MPA), compared with placebo in healthy postmenopausal women.¹¹³ Patients in the intervention arm were found to have increased risks of coronary heart disease, breast cancer, stroke, and venous thromboembolic disease, calling for an early halt of the trial.¹¹³ Subsequent post-hoc analyses and extension studies of the WHI, together with large-scale observation studies, enabled better understanding of the risk-vs-benefit profile of different HT types and patient populations. Regarding breast cancer risk, a meta-analysis of 58 studies demonstrated increased breast cancer risk with all types of HT, with the exception of vaginal estrogen. The risk was greater with the use of combined estrogen-progestogen than with estrogen-only preparations and with longer duration of HT.¹¹⁴ Of note, risk profile of HT is determined not only by the type and duration of hormone used but also by the route of administration. For instance, transdermal estrogen bypasses the first pass metabolism in the liver, and evidence suggests that it does not significantly increase the risk of venous thromboembolism.^{115,116}

Tibolone is another hormone-based agent that is used to treat VMS. It is currently not approved by the FDA and hence not available in the United States.¹¹⁷ It is a synthetic steroid

that has estrogenic, progestogenic, and androgenic effects.¹¹⁸ Because of its progestogenic effect, additional progestogen is not required.¹¹⁸ Tibolone has been shown to be more effective than placebo but less effective than HT in reducing VMS.¹¹⁹ It carries several risks, such as an increased risk of incident breast cancer in women with history of breast cancer, but not in women without prior history of breast cancer.^{119,120} There is also evidence suggesting that it increases the risk of stroke.¹¹⁹ It is currently not recommended as first-line treatment of VMS.⁴

Taking the findings of the abovementioned studies into account, systemic HT is generally not recommended to treat VMS in patients with hormone-sensitive cancers or estrogen receptor positive tumors (such as certain breast, endometrial, and ovarian cancers).^{4,47} Low-dose vaginal estradiol is now a feasible consideration as second-line therapy for urogenital symptoms in patients with history of breast cancer, but it is not an effective treatment for VMS.¹²¹ In patients with active prostate cancer, testosterone therapy should be avoided. Certain guidelines, however, have now given some provision for exploration of testosterone therapy as a treatment for hypogonadism in patients with treated low-risk prostate cancer, although the limitation lies in the lack of long-term safety data.^{19,122} While studies evaluating the use of estrogen-containing HT in men with VMS demonstrated significant improvement in symptoms, gynecomastia was common side effect.¹⁷ Progestogen-based treatments such as megestrol acetate and MPA have also been shown to effectively alleviate VMS in both breast cancer and prostate cancer patients.¹²³⁻¹²⁵ A 400 mg dose of intramuscular MPA, for example, has been demonstrated to provide sustained improvement in VMS in a cohort that included breast cancer survivors during the 6 weeks of observation.¹²⁴ Prostate cancer patients receiving oral MPA of 20 mg daily achieved greater reduction of VMS than those receiving venlafaxine.¹²⁵ Logically, any form of HT should only be prescribed after thorough discussion with the patient, and full disclosure of risks versus benefits. More detailed information pertaining to the safety of HT in each cancer type, and guideline recommendations can be found in [Table 4](#).

For most patients with history of a cancer that is not hormone-sensitive, on the other hand, HT can be a viable option. It should be actively considered in younger women and childhood cancer survivors to prevent bone loss from estrogen deficiency.¹⁴¹ Nonetheless, by virtue of the systemic effects of cancer and sequelae of cancer treatments, cancer patients may be more susceptible to adverse events of HT. For example, cancer patients are at increased risk of developing venous thromboembolism and cardiovascular events.¹⁴²⁻¹⁴⁴ Women with previous chest radiation for Hodgkin lymphoma have increased risk of breast cancer.¹⁴⁵ Furthermore, increased breast cancer risk has been well-described in a number of populations, including those with known mutation in BRCA 1 or BRCA 2 gene and those with certain familial cancer syndromes such as Li-Fraumeni syndrome.^{146,147} Reassuringly, some of these concerns have been addressed by prospective studies. Observational evidence suggests that HT use does not further increase risk of breast cancer in BRCA 1 and BRCA 2 mutation carriers without known cancer, who are status-post risk-reducing bilateral salpingo-oophorectomy.^{148,149}

The current consensus states that in the majority of low-risk VMS patients from the general population, below the age of 60 or within 10 years of menopause onset, the benefits

Table 3. Summary of nonpharmacological interventions in treatment of VMS.

Intervention	Background	Summary of evidence	Guideline recommendations
Weight loss	High BMI, ⁵¹⁻⁵³ weight gain after cancer diagnosis, ^{54,55} increased waist circumference ⁵² have been identified as possible risk factors for VMS.	Cohort studies evaluating the effect of weight loss on VMS have yielded inconsistent results. ^{52,56} Randomized controlled trials have more consistently demonstrated that weight loss from dietary intervention and physical activity could significantly improve frequency and severity of VMS. ⁵⁷⁻⁶⁰	Recommended by NAMS ⁴⁶ (Limited evidence, Levels II-III) and NCCN ⁴⁸
Exercise	Early studies showed that exercise triggered VMS in symptomatic women. ²⁵ Observational studies showed women with regular physical activity were less likely to develop severe VMS ⁶¹	A cochrane review in 2014 and a pooled analysis in 2015 found insufficient evidence to demonstrate the efficacy of exercise in treating VMS. ^{62,63} Since then, some studies have shown that yoga, resistance training, training program, and stretching could improve VMS, ⁶⁴⁻⁶⁷ but others demonstrated no significant benefit. ⁶⁸	Not recommended by NAMS ⁴⁶ for VMS (insufficient/poor evidence, Level II) Recommended by NCCN ⁴⁸
Smoking cessation	In observational studies, former and current smoking have been found to increase risk of VMS in menopausal women ⁶⁹⁻⁷¹	Longitudinal data demonstrated that early smoking cessation (before age 40) ⁷¹ and longer duration of smoking cessation (more than 5 years) were associated with lower risk of VMS, ^{71,72} but there is a lack of interventional studies to evaluate such effect.	Recommended by ES ⁴ to address smoking-cessation during menopause transition
Cognitive-behavioral therapy (CBT)	CBT combines cognitive and behavioral strategies to manage a number of disorders. ⁷³ A cognitive model has been described to explain symptom perception and behavioral response to VMS. ⁷⁴	Evidence from randomized controlled trials supports the use of CBT in treating VMS, including in breast cancer survivors. ⁷⁵ A variety of delivery methods have proven to be effective, including self-guided therapy, remote therapy (via telephone and internet), and group therapy, administered by clinical psychologists or specialist nurses. ⁷⁶⁻⁷⁸	Recommended by NAMS ⁴⁶ (Level I), NCCN, ⁴⁸ ESO/ESMO ⁷⁹
Clinical hypnosis	Clinical hypnosis is a form of mind-body therapy that makes use of guided technique to achieve a relaxed state. It has been explored in the management of various cancer related symptoms. ^{80,81}	Randomized controlled studies evaluating clinical hypnosis in postmenopausal women and breast cancer survivors have demonstrated significant reduction of hot flash frequency and score. ^{82,83}	Recommended by NAMS ⁴⁶ (Level 1), NCCN ⁴⁸
Stellate ganglion block (SGB)	SGB involves sympathetic block by injecting anesthetic agent at C6 or C7 vertebral level. It has been used to treat a variety of conditions including pain syndrome. ⁸⁴ Complications are rare and include injury to nerves, blood vessels, esophagus, trachea, lungs and allergic reactions, etc. ^{84,85}	Prospective studies evaluating SGB on VMS in postmenopausal women and breast cancer survivors have yielded positive results, but the duration of response to each administration of SGB and timing of repeat block remain unclear. ^{86,87}	Recommended by NAMS ⁴⁶ (Levels II-III)—careful evaluation suggested, given its risks and adverse events
Acupuncture	Acupuncture is a form of complementary therapy that involves applying fine needles or pressure to acupoints of skin. ⁸⁸ It has been used to manage a number of cancer related symptoms. ⁸⁹	Prospective studies have evaluated the efficacy of acupuncture on VMS in both postmenopausal women and cancer survivors. ^{90,91} Acupuncture has been shown to reduce VMS in some but not all postmenopausal women. ^{92,93} Factors associated with response to acupuncture have not been consistently established. ⁹⁴ When compared with sham acupuncture, the superiority of true acupuncture has not been consistently proven. ⁹⁵⁻⁹⁷	Not recommended by NAMS ⁴⁶ (Level I for traditional acupuncture, Level II for electroacupuncture) Recommended by NCCN ⁴⁸ and ESO/ESMO (Level I/B) ⁷⁹
Soy foods	Isoflavones from soy food products are phytoestrogens which bind to ERs, with greater affinity for ER α than ER β . They have estrogen-agonist and estrogen-antagonist properties. ⁹⁸ Questions have previously been raised regarding phytoestrogen consumption and breast cancer risk. ⁹⁹	Soy consumption has been demonstrated to have either a benefit ¹⁰⁰ or no significant effect on VMS. ^{101,102} Considerations in cancer patients: In breast cancer patients, overexpression of genes involved in cell proliferation was seen in those taking soy supplementation. ¹⁰³ However, recent studies including the Global Cancer Update Programme suggested that soy intake was associated with a reduced breast-cancer specific mortality and recurrence. ^{104,105}	Not recommended by NAMS ⁴⁶ (Level II)
Black cohosh	Black cohosh, or <i>Actaea racemosa</i> L., is a herbal supplement belonging to the buttercup family. ¹⁰⁶ The mechanism of action of black cohosh appears to be mediated via the opioid receptors, as opposed to ER which was previously thought to be a candidate. ¹⁰⁶	A cochrane review in 2012 concluded that there was insufficient evidence for black cohosh in treating VMS. ¹⁰⁷ Following cases of hepatotoxicity being reported in black cohosh users, cautionary statement is required for black cohosh products. ¹⁰⁸ Considerations in cancer patients: No known association between black cohosh and increased breast cancer risk has been demonstrated. ^{109,110}	Not recommended by NAMS ⁴⁶ (Level I)

Abbreviations: BMI, body mass index; CBT, cognitive-behavioral therapy; ER, estrogen receptor; ES, endocrine society; ESO/ESMO, European School of Oncology/European Society of Medical Oncology; NAMS, North American Menopause Society; NCCN, National Comprehensive Cancer Network; SGB, stellate ganglion block; VMS, vasomotor symptom.

Table 4. Considerations and guideline recommendations on use of HT in VMS management based on cancer type.

Cancer type	Evidence and considerations	Relevant guideline recommendations
Breast cancer	<p>Safety of HT in disease-free patients with previously treated breast cancer: Increased risk of new breast cancer event:</p> <ul style="list-style-type: none"> • HABITS (N = 442): Duration of HT 2 years. (E or E + P) vs non-HT. At median 4 years follow-up, HR = 2.4, 95% CI, 1.3-4.2¹²⁶ Of note: HT arm had increased risk of local recurrences or contralateral breast cancer, but not distal metastasis. • LIBERATE (N = 3098): Tibolone vs placebo. At median 3.1 years follow-up, HR = 1.40, 95% CI, 1.14-1.70¹²⁰ <p>No significantly increased risk of new breast cancer event:</p> <ul style="list-style-type: none"> • Stockholm trial (N = 378): Mean duration of HT 2.6 years. (E or E + P (MPA)) vs vaginal estrogen. At median 10.8 years follow-up, HR = 1.3; 95% CI, 0.9-1.9¹²⁷ <p>Meta-analyses and systemic reviews of interventional and observational studies evaluating the effect of HT on risk of recurrence of breast cancer or new cancer events have led to inconsistent results.¹²⁸⁻¹³⁰</p>	<p>Systemic HT not recommended:</p> <ul style="list-style-type: none"> • ES 2015⁴ • ACO/ASCO 2016¹³¹ • NAMS 2022⁴⁷ (<i>If VMS severe and unresponsive to nonhormone options, HT may be considered following discussion with oncologist and assessment of risk and benefits</i>) • NCCN 2022⁴⁸
Endometrial cancer	<p>A Cochrane Review of 7 RCTs and 2190 participants concluded that there a lack of high-quality evidence on the safety of HT in patients with previously treated endometrial cancer.¹³²</p>	<p>Systemic HT not recommended:</p> <ul style="list-style-type: none"> • ES 2015⁴ • NAMS 2022⁴⁷ (<i>Not recommended in high-grade, advanced-stage endometrial cancers or in endometrial stromal sarcomas or leiomyosarcomas. HT may be used to treat bothersome VMS in women with low-grade, stage I endometrial cancer after hysterectomy, if no improvement with nonhormone therapies, following consultation with oncologist.</i>) • NCCN 2022⁴⁸ (<i>Relatively contraindicated in survivors high-risk endometrial cancer</i>)
Ovarian cancer	<p>Systematic reviews and meta-analyses reviewing use of HT in ovarian cancer survivors did not report reduced survival in those who received HT.^{133,134}</p> <p>There is currently a lack of high-quality data detailing the safety of HT in specific subtypes of ovarian cancers.</p>	<p>Systemic HT not recommended:</p> <ul style="list-style-type: none"> • ES 2015⁴ • NAMS 2022⁴⁷ (<i>Not recommended in hormone-dependent cancers including granulosa-cell tumour and serous carcinoma. HT may be considered in symptomatic women with tumours of low-malignant potential which have been completely resected.</i>)
Prostate cancer	<p>Testosterone replacement:</p> <p>There is currently a lack of good-quality data evaluating the safety of androgen in patients with history of prostate cancer, but an RCT is underway to assess this.¹³⁵</p> <p>Other types of HT:</p> <ul style="list-style-type: none"> • Data from RCT reported effectiveness of medroxyprogesterone acetate and cyproterone acetate for treatment of VMS in prostate cancer patients on GnRH analogue.¹²⁵ • While megestrol acetate is effective in reducing VMS,¹³⁶ safety appears variable—most studies report good tolerability and safety, but there are cases reporting rising PSA while on megestrol acetate^{123,137} 	<p>Testosterone not recommended:</p> <ul style="list-style-type: none"> • ES 2018¹³⁸ • NCCN 2022⁴⁸ <p>Other comments:</p> <ul style="list-style-type: none"> • EAU 2024^{19,139} - Androgens contraindicated in men with active prostate cancer. Possible use of testosterone therapy in symptomatic hypogonadal men with previously treated prostate cancer which are EAU low-risk for recurrence, after full discussion with patient. <i>*Note: this comment pertains to hypogonadism and is not specific to VMS</i> <p>Regarding use of other types of HT and agents</p> <ul style="list-style-type: none"> • NCCN 2022⁴⁸ [<i>HT (medroxyprogesterone, cyproterone acetate, estrogen) in appropriate candidates with referral to appropriate specialists.</i>] • CUA 2022¹⁴⁰ (<i>Agents which may be considered: medroxyprogesterone acetate, megestrol acetate, cyproterone acetate, gabapentin, venlafaxine.</i>)
<p>Collectively these recommendations highlight the concerns with using testosterone in patients with history of prostate cancer, as well as lack of long-term safety data. While HT may be considered for low-risk patients with successfully treated prostate cancer and undetectable PSA level, a watch period to ensure absence of evidence of disease is required before HT commencement.</p>		

Abbreviations: ACO/ASCO, American Cancer Society/American Society of Clinical Oncology; CEE, Conjugated Equine Estrogen; CUA, Canadian Urological Association; E, Estrogen; E + P, Estrogen and Progestogen; EAU, European Association of Urology; ES, Endocrine Society; HABITS, Hormonal Replacement After Breast Cancer—Is it Safe?; HR, Hazard Ratio; LIBERATE, Livial Intervention following Breast cancer Efficacy, Recurrence, and Tolerability Endpoints; MPA, Medroxyprogesterone Acetate; NAMS, North American Menopause Society; NCCN, National Comprehensive Cancer Network; PSA, Prostate-Specific Antigen; RCT, Randomized Controlled Trial; WHI, Women's Health Initiative.

of HT will outweigh the risks.⁴ Given the complexity of the management considerations in cancer patients however, HT should be offered only after careful assessment of risks versus benefits. The Endocrine Society suggests exercising caution when considering HT in patients with intermediate breast cancer risk, and to avoid HT in those with high risk for breast cancer, as stratified by the National Cancer Institute Breast Cancer Risk Assessment Tool.^{4,150} If a decision for HT is made, it should be prescribed based on recommendations from societal guidelines. The dose of HT used should be the lowest needed to achieve therapeutic response.^{4,47}

Nonhormone therapy

There is growing evidence supporting the utilization of nonhormone treatments in cancer patients with VMS. Pharmacological agents that have been evaluated include antidepressants, GABA analogues, clonidine, oxybutynin, etc. The onset of action of these drugs is rapid, usually within 1-2 weeks.⁴⁶ When examining the efficacy of these agents, it is important to note the significance of placebo effect in trials. Typically, placebo alone can achieve ~20%-60% improvement in outcome measures in VMS studies.⁴⁶ Interestingly, a lower placebo response is seen in studies with breast cancer patients.¹⁵¹ As many of these drugs target neurotransmission pathways, older adults can be particularly susceptible to adverse effects. Currently, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentin, and fezolinetant are the agents preferentially recommended by NAMS with level I evidence and oxybutynin with level I-II evidence.⁴⁶ Suggested considerations in prescribing these drugs are summarized in Table 5.

Antidepressants

Selective serotonin reuptake inhibitors (eg, escitalopram, citalopram, and paroxetine) and SNRIs (eg, duloxetine and venlafaxine) are the largest groups of nonhormone therapies studied, both in healthy women and cancer patients with VMS.¹⁷⁰⁻¹⁷² They can reduce hot flash frequency by up to 58% and hot flash scores by up to 65%.^{170,171,173} Selective serotonin reuptake inhibitors and SNRIs have also been compared with other drugs such as clonidine.¹⁷⁴ As there is no convincing evidence supporting the superiority of any these agents over others, tolerability and side-effect profile are important determinants of treatment outcome. At present, paroxetine (Brisdelle, 7.5 mg) is the only antidepressant approved by the FDA for the treatment of moderate-to-severe VMS associated with menopause.¹⁷⁵ Its efficacy has also been demonstrated in patients with breast and gynecological cancers.^{172,176} However, due to its strong inhibition of the cytochrome P450 2D6 (CYP2D6) enzyme, paroxetine should be avoided in patients on tamoxifen treatment. Active metabolites of tamoxifen can be decreased by up to 64% in patients taking paroxetine.¹⁵⁶ Likewise, fluoxetine, another strong CYP2D6 inhibitor, should also be avoided in tamoxifen-treated patients. In older adults, venlafaxine and paroxetine may not be the initial drug of choice due to risk of withdrawal.¹⁶⁰ Escitalopram and citalopram may be the preferred drugs in this age group due to their lower side effect profile. Compared with citalopram, there are fewer cardiac side effects with escitalopram (eg, QTc prolongation).^{177,178} Drowsiness and dizziness are common adverse effects of SSRIs and SNRIs and can be potentially managed by adjusting the timing of administration.¹⁷⁹ Taking the medication at night may not only alleviate symptoms

from nocturnal VMS more effectively but also mitigate side effects such as nausea. Caution should be exercised in patients with hyponatremia, which can be associated with both cancer and SSRI use.^{152,153} Other adverse effects of antidepressants include sexual dysfunction and weight gain, which may overlap with symptoms of menopause, and should be considered in discussion on VMS treatment options.^{180,181} Regardless of the drug chosen, the lowest possible dose necessary for symptom relief should be used. Upon decision to stop the therapy, tapering should be done to avoid withdrawal symptoms.¹⁷⁹

GABA analogues

γ -Aminobutyric acid (GABA) analogues such as gabapentin and pregabalin have been studied in the treatment of VMS in patients with and without cancer. Gabapentin, but not pregabalin, is currently recommended by NAMS for treatment of VMS.⁴⁶ At a dose of 900 mg per day, gabapentin can reduce hot-flash frequency by 44% and severity by 46% in breast cancer patients.¹⁸² This effect appears to be dose dependent, as the 300 mg per day treatment arm achieved a smaller improvement in frequency and severity scores. A trial of pregabalin demonstrated reduction of hot flash score by 65% in the 75 mg twice daily regimen, and by 71% in the 150 mg twice daily regimen. These effects, however, are on a background of 50% placebo response.¹⁸³ In addition to alleviating VMS, gabapentin has also been shown to improve anxiety scores in breast cancer survivors with anxiety.¹⁸⁴ Considering these findings and its neuropathic pain-alleviating property, gabapentin is a viable option in cancer patients with VMS and pain or anxiety. Weight gain is a potential adverse effect which should be discussed with patients.¹⁸⁵

Clonidine

Clonidine is a centrally acting α_2 -adrenergic agonist primarily used in treatment of hypertension and attention deficit hyperactivity disorder. The ability of clonidine, both oral and transdermal, to reduce the frequency of hot flashes was demonstrated decades ago.¹⁸⁶⁻¹⁸⁸ In breast cancer patients with VMS, clonidine can reduce the frequency of hot flashes by 38%.¹⁸⁹ Dry mouth, lethargy, nausea, and difficulty in sleeping are the most frequently reported side effects.^{174,188,190} Owing to its ability to reduce blood pressure, clonidine may be considered in patients with concomitant hypertension but should be used with caution in patients who are prone to dizziness and falls, such as older adults.

Oxybutynin

Oxybutynin, an anticholinergic drug primarily prescribed for overactive bladder, can effectively reduce hot flash scores and frequency when administered at doses of 2.5 and 5 mg twice daily.¹⁹¹ However, its anticholinergic properties give rise to side effects such as dry mouth, difficulty urinating and constipation, all of which may be particularly problematic in older adults. Additionally, oxybutynin can increase risk for falls and delirium in this population.¹⁹² When a dose of 15 mg daily dose was used, the rate of adverse events increased significantly, leading to drug discontinuation in 6.8% of participants in a randomized controlled trial.¹⁹³

Fezolinetant

Following the elucidation of the role of KNDy neuron in the development of VMS, neurokinin receptors naturally became potential drug targets for management of

Table 5. Summary of pharmacological interventions in treatment of VMS.

Medication	Commonly used dose	Considerations in specific patients populations
Hormone therapy	<p>*Note: many options are available, for more detailed description of regimens, refer to ES⁴ and NAMS⁴⁷ guidelines</p> <p>Systemic estrogen therapy—Transdermal estradiol patch (0.025-0.1 mg) once or twice weekly</p> <p>With progestogen therapy in women with intact uterus—Oral micronized progesterone 200 mg once daily cyclically (~12 days for 28-day cycle) or 100 mg once daily continuously</p>	<p>Special patient population (see Table 4 for details)</p> <ul style="list-style-type: none"> • Cancer patients—HT generally contraindicated in hormone-sensitive cancers • Older adults—avoid starting in women over the age of 60 and more than 10 years from menopause onset <p>Other contraindications include unexplained vaginal bleeding, history of cardiovascular disease, venous thromboembolism, arterial thromboembolic disease, liver impairment, thrombophilic disorders, increased risk of cardiovascular disease, increased risk of breast cancer, etc. (list is not exhaustive, refer to societal guidelines for further details).^{4,47}</p>
Antidepressants	<p>Escitalopram (SSRI)—start with 5-10 mg once daily, increase to 20 mg once daily after 4 weeks as needed</p> <p>Citalopram (SSRI)—start with 10 mg once daily, increase to 20 mg once daily after 1 week as needed</p> <p>Paroxetine (SSRI)—start with 7.5 mg (single dose capsule with no titration needed) or 10 mg/day, increase to 25 mg/day as needed, depending on type of preparation</p> <p>Venlafaxine (SNRI)—start with 37.5 mg/day, increase to 75 mg/day as needed</p>	<p>Special patient population</p> <ul style="list-style-type: none"> • Cancer patients—hyponatremia can be associated with both cancer and SSRI use.^{152,153} Paroxetine has weak anticholinergic effect and may cause/worsen dry mouth and constipation.¹⁵⁴ Both SSRI and SNRIs can cause nausea soon after initiation, but symptom usually improves.¹⁵⁵ • Breast cancer patients—avoid paroxetine in patients taking tamoxifen.¹⁵⁶ • Older adults—higher risk of dose-dependent increase in BP induced by SNRI,¹⁵⁷ hyponatremia induced by SSRI,¹⁵⁸ QT interval prolongation induced by citalopram and escitalopram,¹⁵⁹ risk of symptomatic withdrawal if patient has tendency to omit/stop medication (especially with paroxetine and venlafaxine)¹⁶⁰ <p>Contraindications: SSRIs and SNRIs contraindicated in patients with history of serotonin syndrome, and current use of monoamine oxidase inhibitors.⁴⁶</p> <p>Drug interactions: antiemetics (5HT₃ antagonists such as ondansetron), monoamine oxidase inhibitors, opioids¹⁶¹</p>
GABA analogues	Gabapentin—start with 100-300 mg/day with first dose given at bedtime, gradual increase to 900 mg/day in divided doses as needed. Higher doses may be potentially given, but most trials use dose up to 900 mg/day	<p>Special patient population</p> <ul style="list-style-type: none"> • Older adults—gabapentin is generally safe, but may cause dose-dependent dizziness or drowsiness.¹⁶² Use with caution in patients at risk of falls. Consider evening dosing to minimize impact of adverse effects. Start low dose and increase slowly. • Renal impairment—Dose adjustment is needed in patients with renal impairment. <p>Drug interactions: opioids (may enhance CNS depression effect)</p>
Clonidine	0.05 mg twice daily. Discontinue treatment if no improvement after 2-4 weeks	<p>Special patient population</p> <ul style="list-style-type: none"> • Older adults—clonidine can cause hypotension and bradycardia.^{163,164} Use with caution in patients at risk of falls. <p>Drug interactions—beta blockers (risk of bradycardia), hydroxyzine (may enhance CNS depression effect)¹⁶⁵</p>
Oxybutynin	Immediate release 2.5-5 mg twice/day or Extended release 5-15 mg/day	<p>Special patient population</p> <ul style="list-style-type: none"> • Older adults—increased risk of anticholinergic effects such as CNS disturbance (confusion, agitation, cognitive impairment, drowsiness, dizziness), urinary retention, constipation, visual disturbance, tachycardia¹⁶⁶
Fezolinetant	45 mg/day	<p>Newly approved and limited data available. From SKYLIGHT 1 trial, treatment-emergent adverse reactions included headache and a small number of participants with abnormal ALT or AST.¹⁶⁷ It is recommended to measure liver enzyme levels at baseline and monthly for the first 3 months, then at months 6 and 9 following initiation of treatment.¹⁶⁸</p> <p>Contraindications: avoid in patients with cirrhosis, severe renal impairment, or end stage renal disease.</p> <p>Drug interactions—Fezolinetant is metabolized by CYP1A2 and should be avoided in patients on CYP1A2 inhibitors¹⁶⁹</p>

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CNS, central nervous system; RCT, randomized controlled trial; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

VMS. Fezolinetant, a selective NK3 receptor antagonist, demonstrated greater than 61% in reduction of hot-flash frequency in SKYLIGHT I trial.¹⁶⁷ Fezolinetant is now approved by the FDA for treatment of moderate to severe hot flashes, at a dose of 45 mg once daily.¹⁹⁴ Encouragingly, a recent meta-analysis revealed that fezolinetant reduced VMS frequency, demonstrating comparable efficacy to HT,

and significantly exceeding the reduction seen in other nonhormone agents.¹⁹⁵ Furthermore, longer studies have shown that the drug appeared to be safe with a low rate of drug discontinuation.^{196,197} Adverse effects of fezolinetant include increased alanine transaminase (ALT) or aspartate transaminase (AST) levels, which is typically mild, transient, with most of the ALT and AST elevations being no

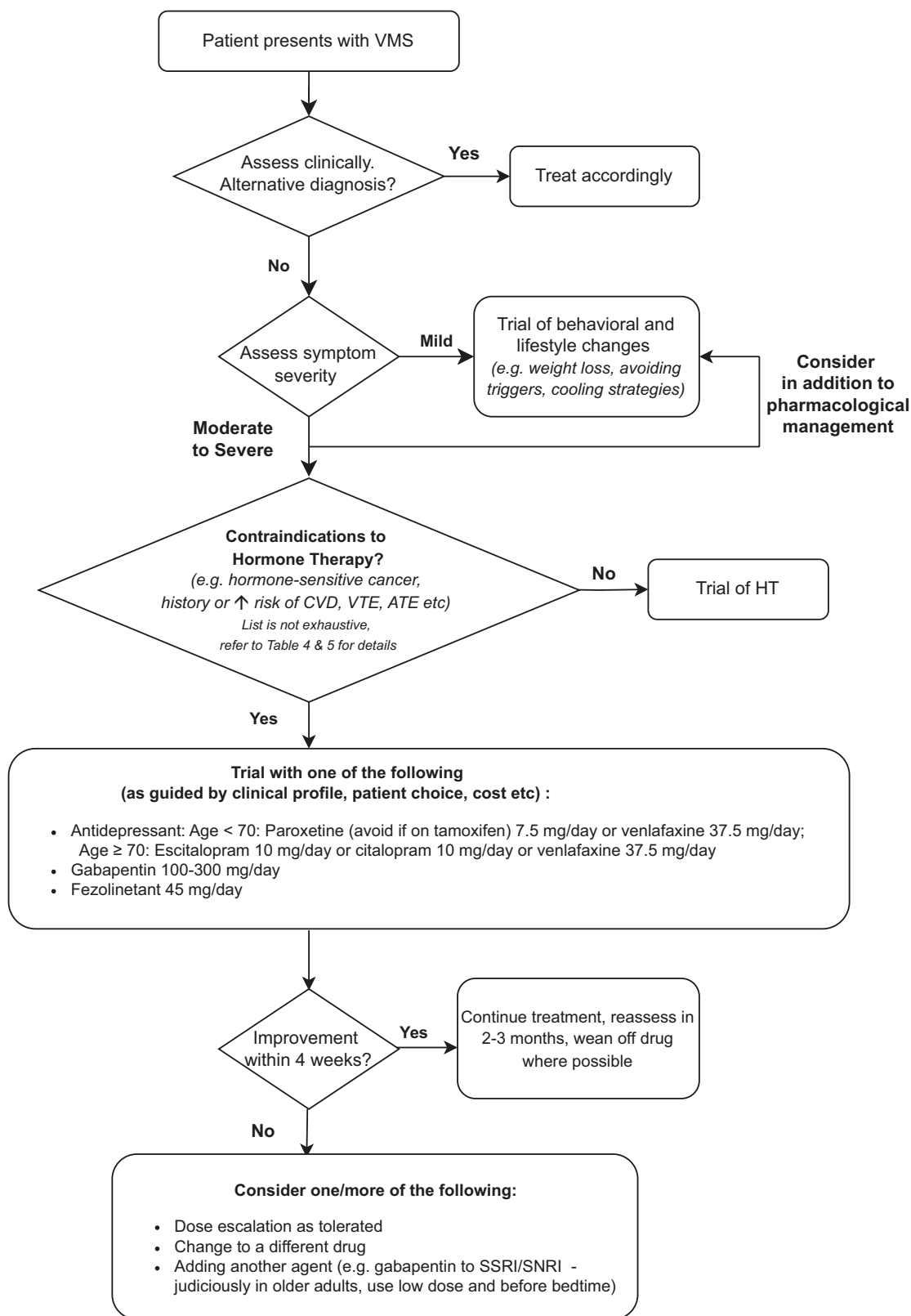


Figure 2. Suggested approach to a cancer patient presenting with VMS. Abbreviations: ATE, arterial thromboembolism; CVD, cardiovascular disease; HT, hormone therapy; SNRI, serotonin norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; VMS, vasomotor symptoms; VTE, venous thromboembolism.

greater than 3 times the upper limits of normal.^{167,198} At present, there is no data on the effect and safety of fezolinetant in cancer survivors.

Other novel agents

A few other drugs have been developed to block the activation of the NK3 receptor. Elinzanetant, a dual neurokinin 1

and neurokinin 3 receptor antagonist, also appeared to be well tolerated in phase II trials, with several phase III trials being conducted currently.¹⁹⁹ Q-122 is an oral agent, which can reduce KNDy neuron activation independent of the NK3 receptor pathway, and a recent phase 2 study demonstrated significant reduction in VMS compared with placebo.²⁰⁰ Notably, the study was conducted in breast cancer patients on tamoxifen or AI. Collectively, the development of these novel therapeutic agents has brought about great promise to the options that cancer patients with VMS may have in the near future.

Suggested approach in clinical practice

Based on the current understanding of efficacy and safety of drugs used to treat VMS and the authors' collective clinical experience, we have proposed the following clinical approach to VMS in cancer patients (Figure 2). As most of the trials on nonhormone therapies have short monitoring intervals of 4 weeks, and follow-up duration of under 6 months, we suggest that patients who are commenced on such treatment be reviewed regularly. If a therapy is deemed to be ineffective at the recommended dose (which is often a low dose), there may be limited value in increasing the dose further. As the overarching aim of management of VMS is to improve the quality of life of cancer survivors, the side effect profile of any pharmacological agent should be weighed against the clinical benefit.

Conclusion

Given the high prevalence of VMS in cancer patients, it would be valuable for managing clinicians such as oncologists, endocrinologists, and primary care providers to routinely ask about VMS and be familiar with the approach to VMS management. The field is evolving, with richer long-term data now available on the risks and benefits of HT in patients with specific cancer types. Nonhormone therapies have emerged as effective alternatives for many and are now incorporated into major guidelines. Furthermore, the emergence of novel therapies such as fezolinetant has provided additional treatment options, thereby fostering a more promising outlook for cancer survivorship.

Acknowledgments

Figure 1 created with BioRender.com (Agreement Number FQ272FQU88).

Figure 2 created with draw.io (v24.7.1).

Author contributions

Ling Zhu (Writing—original draft, Writing—review & editing), Tammy T. Hsieh (Writing—original draft, Writing—review & editing), Tara K. Iyer (Writing—original draft, Writing—review & editing), Alicia K. Morgans (Conceptualization, Writing—original draft, Writing—review & editing), Ole-Petter R. Hamnvik (Conceptualization, Writing—original draft, Writing—review & editing)

Funding

None.

Conflict of interest

T.K.I. reports advisory roles at Astellas and Bayer. A.K.M. reports advisory roles at Astellas, AstraZeneca, Bayer, Exelixis, Lantheus, Curium, Merck, Myovant, MacroGenics, Pfizer, Novartis, SMPA, Sanofi, and Telix, and research funding from Astellas, AstraZeneca, Bayer, Lantheus, Curium, Myovant, Pfizer, Novartis, SMPA, and Telix. All other authors have no conflicts of interest.

Data Availability

No new data were generated in this research. Data underlying this article are available on request.

References

- Allemani C, Matsuda T, Di Carlo V, et al; CONCORD Working Group. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;391:1023-1075. [https://doi.org/10.1016/S0140-6736\(17\)33326-3](https://doi.org/10.1016/S0140-6736(17)33326-3)
- Dev R, Hui D, Del Fabbro E, et al. Association between hypogonadism, symptom burden, and survival in male patients with advanced cancer. *Cancer*. 2014;120:1586-1593. <https://doi.org/10.1002/cncr.28619>
- Faw CA, Brannigan RE. Hypogonadism and cancer survivorship. *Curr Opin Endocrinol Diabetes Obes*. 2020;27:411-418. <https://doi.org/10.1097/MED.0000000000000583>
- Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100:3975-4011. <https://doi.org/10.1210/jc.2015-2236>
- Woods NE, Mitchell ES. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. *Am J Med*. 2005;118:14-24. <https://doi.org/10.1016/j.amjmed.2005.09.031>
- Spetz A-CE, Fredriksson MG, Hammar ML. Hot flushes in a male population aged 55, 65, and 75 years, living in the community of Linköping, Sweden. *Menopause*. 2003;10:81-87. <https://doi.org/10.1097/00042192-200310010-00013>
- Avis NE, Crawford SL, Greendale G, et al; Study of Women's Health across the Nation. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med*. 2015;175:531-539. <https://doi.org/10.1001/jamainternmed.2014.8063>
- Cole KM, Clemons M, Alzahrani M, et al. Vasomotor symptoms in early breast cancer—a “real world” exploration of the patient experience. *Support Care Cancer*. 2022;30:4437-4446. <https://doi.org/10.1007/s00520-022-06848-3>
- Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249. <https://doi.org/10.3322/caac.21660>
- Francis PA, Regan MM, Fleming GF, et al; SOFT Investigators. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2015;372:436-446. <https://doi.org/10.1056/NEJMoa1412379>
- Osborne CK. Tamoxifen in the treatment of breast cancer. *N Engl J Med*. 1998;339:1609-1618. <https://doi.org/10.1056/NEJM199811263392207>
- Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med*. 2003;349:1793-1802. <https://doi.org/10.1056/NEJMoa032312>
- Mao D, Hachem H, Chang H, et al. Treatment interruption and discontinuation of hormonal therapy in hormone receptor-positive

- breast cancer patients. *Breast Cancer Res Treat.* 2020;184:665-674. <https://doi.org/10.1007/s10549-020-05892-z>
14. Davies S, Voutsadakis IA. Adherence to adjuvant hormonal therapy in localised breast cancer. *Eur J Cancer Care (Engl).* 2022;31:e13729. <https://doi.org/10.1111/ecc.13729>
 15. Zeng E, He W, Smedby KE, Czene K. Adjuvant hormone therapy-related hot flashes predict treatment discontinuation and worse breast cancer prognosis. *J Natl Compr Canc Netw.* 2022;20:683-689.e2. <https://doi.org/10.6004/jnccn.2021.7116>
 16. Fleming L, Agnew S, Peddie N, et al. The impact of medication side effects on adherence and persistence to hormone therapy in breast cancer survivors: a quantitative systematic review. *Breast.* 2022;64:63-84. <https://doi.org/10.1016/j.breast.2022.04.010>
 17. Jones JM, Kohli M, Loprinzi CL. Androgen deprivation therapy-associated vasomotor symptoms. *Asian J Androl.* 2012;14:193-197. <https://doi.org/10.1038/aja.2011.101>
 18. Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Perimenopause as a neurological transition state. *Nat Rev Endocrinol.* 2015;11:393-405. <https://doi.org/10.1038/nrendo.2015.82>
 19. Cornford P, Tilki D, van den Bergh RCN, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. *European Association of Urology*; 2024. Available at <https://uroweb.org/guidelines/prostate-cancer>. Accessed July 15, 2024.
 20. Simpson ER. Role of aromatase in sex steroid action. *J Mol Endocrinol.* 2000;25:149-156. <https://doi.org/10.1677/jme.0.0250149>
 21. Smith JA. Management of hot flushes due to endocrine therapy for prostate carcinoma. *Oncology.* 1996;10:1319-22; discussion 1324.
 22. Engstrom CA, Kasper CE. Physiology and endocrinology of hot flashes in prostate cancer. *Am J Mens Health.* 2007;1:8-17. <https://doi.org/10.1177/1557988306294162>
 23. Tan CL, Knight ZA. Regulation of body temperature by the nervous system. *Neuron.* 2018;98:31-48. <https://doi.org/10.1016/j.neuron.2018.02.022>
 24. Mekjavić IB, Sundberg CJ, Linnarsson D. Core temperature “null zone”. *J Appl Physiol Bethesda Md* 1985. 1991;71:1289-1295.
 25. Freedman RR, Krell W. Reduced thermoregulatory null zone in postmenopausal women with hot flashes. *Am J Obstet Gynecol.* 1999;181:66-70. [https://doi.org/10.1016/s0002-9378\(99\)70437-0](https://doi.org/10.1016/s0002-9378(99)70437-0)
 26. Rance NE, Young WS. Hypertrophy and increased gene expression of neurons containing neurokinin-B and substance-P messenger ribonucleic acids in the hypothalamus of postmenopausal women. *Endocrinology.* 1991;128:2239-2247. <https://doi.org/10.1210/endo-128-5-2239>
 27. Padilla SL, Johnson CW, Barker FD, Patterson MA, Palmiter RD. A neural circuit underlying the generation of hot flashes. *Cell Rep.* 2018;24:271-277. <https://doi.org/10.1016/j.celrep.2018.06.037>
 28. Krajewski-Hall SJ, Miranda Dos Santos F, McMullen NT, Blackmore EM, Rance NE. Glutamatergic neurokinin 3 receptor neurons in the median preoptic nucleus modulate heat-defense pathways in female mice. *Endocrinology.* 2019;160:803-816. <https://doi.org/10.1210/en.2018-00934>
 29. Nelson HD. Menopause. *Lancet.* 2008;371:760-770. [https://doi.org/10.1016/S0140-6736\(08\)60346-3](https://doi.org/10.1016/S0140-6736(08)60346-3)
 30. Melby MK, Lock M, Kaufert P. Culture and symptom reporting at menopause. *Hum Reprod Update.* 2005;11:495-512. <https://doi.org/10.1093/humupd/dmi018>
 31. Freedman RR, Norton D, Woodward S, Cornélissen G. Core body temperature and circadian rhythm of hot flashes in menopausal women. *J Clin Endocrinol Metab.* 1995;80:2354-2358. <https://doi.org/10.1210/jcem.80.8.7629229>
 32. Sievert LL, Reza A, Mills P, et al. Diurnal rhythm and concordance between objective and subjective hot flashes: the hilo women's health study. *Menopause.* 2010;17:471-479. <https://doi.org/10.1097/gme.0b013e3181cbb3c6>
 33. Xu H, Thurston RC, Matthews KA, et al. Are hot flashes associated with sleep disturbance during midlife? Results from the STRIDE cohort study. *Maturitas.* 2012;71:34-38. <https://doi.org/10.1016/j.maturitas.2011.10.003>
 34. Hatcher KM, Smith RL, Chiang C, Flaws JA, Mahoney MM. Nocturnal hot flashes, but not serum hormone concentrations, as a predictor of insomnia in menopausal women: results from the midlife women's health study. *J Womens Health.* 2023;32:94-101. <https://doi.org/10.1089/jwh.2021.0502>
 35. Mohyi D, Tabassi K, Simon J. Differential diagnosis of hot flashes. *Maturitas.* 1997;27:203-214. [https://doi.org/10.1016/s0378-5122\(97\)83974-6](https://doi.org/10.1016/s0378-5122(97)83974-6)
 36. Hannah-Shmouni F, Stratakis CA, Koch CA. Flushing in (neuro) endocrinology. *Rev Endocr Metab Disord.* 2016;17:373-380. <https://doi.org/10.1007/s11154-016-9394-8>
 37. Kupperman HS, Wetchler BB, Blatt MH. Contemporary therapy of the menopausal syndrome. *J Am Med Assoc.* 1959;171:1627-1637. <https://doi.org/10.1001/jama.1959.03010300001001>
 38. Greene JGA. factor analytic study of climacteric symptoms. *J Psychosom Res.* 1976;20:425-430.
 39. Greene JG. Constructing a standard climacteric scale. *Maturitas.* 1998;29:25-31. [https://doi.org/10.1016/s0378-5122\(98\)00025-5](https://doi.org/10.1016/s0378-5122(98)00025-5)
 40. Schneider HP, Heinemann LA, Rosemeier HP, Potthoff P, Behre HM. The Menopause Rating Scale (MRS): reliability of scores of menopausal complaints. *Climacteric.* 2000;3:59-64. <https://doi.org/10.3109/13697130009167600>
 41. Iliodromiti S, Wang W, Lumsden MA, et al. Variation in menopausal vasomotor symptoms outcomes in clinical trials: a systematic review. *BJOG.* 2020;127:320-333. <https://doi.org/10.1111/1471-0528.15990>
 42. Sloan JA, Loprinzi CL, Novotny PJ, et al. Methodologic lessons learned from hot flash studies. *J Clin Oncol.* 2001;19:4280-4290. <https://doi.org/10.1200/JCO.2001.19.23.4280>
 43. Carpenter JS. The Hot Flash Related Daily Interference Scale: a tool for assessing the impact of hot flashes on quality of life following breast cancer. *J Pain Symptom Manage.* 2001;22:979-989. [https://doi.org/10.1016/s0885-3924\(01\)00353-0](https://doi.org/10.1016/s0885-3924(01)00353-0)
 44. Chang H-Y, Jotwani AC, Lai Y-H, et al. Hot flashes in breast cancer survivors: Frequency, severity and impact. *Breast.* 2016;27:116-121. <https://doi.org/10.1016/j.breast.2016.02.013>
 45. Guidance for Industry. *Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation.* 2003. Available at <https://www.fda.gov/files/drugs/published/Estrogen-and-Estrogen-Progestin-Drug-Products-to-Treat-Vasomotor-Symptoms-and-Vulvar-and-Vaginal-Atrophy-Symptoms-%E2%80%94-Recommendations-for-Clinical-Evaluation.pdf>. Accessed June 3, 2023.
 46. “The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society” Advisory Panel. The 2023 nonhormone therapy position statement of The North American Menopause Society. *Menopause N Y N.* 2023;30(6):573-590.
 47. “The 2022 Hormone Therapy Position Statement of the North American Menopause Society” Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause N Y N.* 2022;29:767-794.
 48. Sanft T, Day A, Peterson L, et al. NCCN Guidelines® insights: survivorship, version 1.2022. *JNCCN.* 2022;20:1080-1090. <https://doi.org/10.6004/jnccn.2022.0052>
 49. Marshall-McKenna R, Morrison A, Stirling L, et al. A randomised trial of the cool pad pillow topper versus standard care for sleep disturbance and hot flashes in women on endocrine therapy for breast cancer. *Support Care Cancer.* 2016;24:1821-1829. <https://doi.org/10.1007/s00520-015-2967-3>
 50. Composto J, Leichman ES, Luedtke K, Mindell JA. Thermal comfort intervention for hot-flash related insomnia symptoms in perimenopausal and postmenopausal-aged women: an exploratory study. *Behav Sleep Med.* 2021;19:38-47. <https://doi.org/10.1080/15402002.2019.1699100>
 51. Gallicchio L, Visvanathan K, Miller SR, et al. Body mass, estrogen levels, and hot flashes in midlife women. *Am J Obstet Gynecol.* 2005;193:1353-1360. <https://doi.org/10.1016/j.ajog.2005.04.001>

52. Gold EB, Crawford SL, Shelton JF, et al. Longitudinal analysis of changes in weight and waist circumference in relation to incident vasomotor symptoms: the Study of Women's Health Across the Nation (SWAN). *Menopause*. 2017;24:9-26. <https://doi.org/10.1097/GME.0000000000000723>
53. Saccomani S, Lui-Filho JF, Juliato CR, et al. Does obesity increase the risk of hot flashes among midlife women?: a population-based study. *Menopause*. 2017;24:1065-1070. <https://doi.org/10.1097/GME.0000000000000884>
54. Su HI, Sammel MD, Springer E, et al. Weight gain is associated with increased risk of hot flashes in breast cancer survivors on aromatase inhibitors. *Breast Cancer Res Treat*. 2010;124:205-211. <https://doi.org/10.1007/s10549-010-0802-6>
55. Caan BJ, Emond JA, Su HI, et al. Effect of postdiagnosis weight change on hot flash status among early-stage breast cancer survivors. *J Clin Oncol*. 2012;30:1492-1497. <https://doi.org/10.1200/JCO.2011.36.8597>
56. van Poppel MNM, Brown WJ. "It's my hormones, doctor"--does physical activity help with menopausal symptoms? *Menopause N Y N*. 2008;15:78-85.
57. Huang AJ, Subak LL, Wing R, et al; Program to Reduce Incontinence by Diet and Exercise Investigators. An intensive behavioral weight loss intervention and hot flashes in women. *Arch Intern Med*. 2010;170:1161-1167. <https://doi.org/10.1001/archinternmed.2010.162>
58. Kroenke CH, Caan BJ, Stefanick ML, et al. Effects of a dietary intervention and weight change on vasomotor symptoms in the Women's Health Initiative. *Menopause*. 2012;19:980-988. <https://doi.org/10.1097/gme.0b013e31824f606e>
59. Thurston RC, Ewing LJ, Low CA, Christie AJ, Levine MD. Behavioral weight loss for the management of menopausal hot flashes: a pilot study. *Menopause*. 2015;22:59-65. <https://doi.org/10.1097/GME.0000000000000274>
60. Barnard ND, Kahleova H, Holtz DN, et al. A dietary intervention for vasomotor symptoms of menopause: a randomized, controlled trial. *Menopause*. 2023;30:80-87. <https://doi.org/10.1097/GME.0000000000002080>
61. Di Donato P, Giulini NA, Bacchi Modena A, et al.; Progetto Menopausa Italia Study Group. Factors associated with climacteric symptoms in women around menopause attending menopause clinics in Italy. *Maturitas*. 2005;52:181-189. <https://doi.org/10.1016/j.maturitas.2005.01.008>
62. Daley A, Stokes-Lampard H, Thomas A, MacArthur C. Exercise for vasomotor menopausal symptoms. *Cochrane Database Syst Rev*. 2014;2014:CD006108. <https://doi.org/10.1002/14651858.CD006108.pub4>
63. Guthrie KA, LaCroix AZ, Ensrud KE, et al. Pooled analysis of six pharmacologic and nonpharmacologic interventions for vasomotor symptoms. *Obstet Gynecol*. 2015;126:413-422. <https://doi.org/10.1097/AOG.0000000000000927>
64. Kai Y, Nagamatsu T, Kitabatake Y, Sensui H. Effects of stretching on menopausal and depressive symptoms in middle-aged women: a randomized controlled trial. *Menopause*. 2016;23:827-832. <https://doi.org/10.1097/GME.0000000000000651>
65. Cramer H, Peng W, Lauche R. Yoga for menopausal symptoms-a systematic review and meta-analysis. *Maturitas*. 2018;109:13-25. <https://doi.org/10.1016/j.maturitas.2017.12.005>
66. Baena-García L, Flor-Alemán M, Marín-Jiménez N, Aranda P, Aparicio VA. A 16-week multicomponent exercise training program improves menopause-related symptoms in middle-aged women. The FLAMENCO project randomized control trial. *Menopause*. 2022;29:537-544. <https://doi.org/10.1097/GME.0000000000001947>
67. Berin E, Hammar M, Lindblom H, Lindh-Åstrand L, Spetz Holm A-C. Effects of resistance training on quality of life in postmenopausal women with vasomotor symptoms. *Climacteric*. 2022;25:264-270. <https://doi.org/10.1080/13697137.2021.1941849>
68. Daley AJ, Thomas A, Roalfe AK, et al. The effectiveness of exercise as treatment for vasomotor menopausal symptoms: randomised controlled trial. *BJOG*. 2015;122:565-575. <https://doi.org/10.1111/1471-0528.13193>
69. Jenabi E, Poorolajal J. The association between hot flashes and smoking in midlife women: a meta-analysis. *Climacteric*. 2015;18:797-801. <https://doi.org/10.3109/13697137.2015.1080236>
70. Ziv-Gal A, Smith RL, Gallicchio L, et al. The Midlife Women's Health Study - a study protocol of a longitudinal prospective study on predictors of menopausal hot flashes. *Womens Midlife Health*. 2017;3:4. <https://doi.org/10.1186/s40695-017-0024-8>
71. Anderson DJ, Chung H-F, Seib CA, et al. Obesity, smoking, and risk of vasomotor menopausal symptoms: a pooled analysis of eight cohort studies. *Am J Obstet Gynecol*. 2020;222:478.e1-478.e17. <https://doi.org/10.1016/j.ajog.2019.10.103>
72. Smith RL, Flaws JA, Gallicchio L. Does quitting smoking decrease the risk of midlife hot flashes? a longitudinal analysis. *Maturitas*. 2015;82:123-127. <https://doi.org/10.1016/j.maturitas.2015.06.029>
73. Hofmann SG, Asnaani A, Vonk IJJ, Sawyer AT, Fang A. The efficacy of cognitive behavioral therapy: a review of meta-analyses. *Cognit Ther Res*. 2012;36:427-440. <https://doi.org/10.1007/s10608-012-9476-1>
74. Hunter MS, Mann E. A cognitive model of menopausal hot flashes and night sweats. *J Psychosom Res*. 2010;69:491-501. <https://doi.org/10.1016/j.jpsychores.2010.04.005>
75. Ye M, Shou M, Zhang J, et al. Efficacy of cognitive therapy and behavior therapy for menopausal symptoms: a systematic review and meta-analysis. *Psychol Med*. 2022;52:433-445. <https://doi.org/10.1017/S0033291721005407>
76. Atema V, van Leeuwen M, Kieffer JM, et al. Efficacy of internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. *J Clin Oncol*. 2019;37:809-822. <https://doi.org/10.1200/JCO.18.00655>
77. Ayers B, Smith M, Hellier J, Mann E, Hunter MS. Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flashes and night sweats (MENOS 2): a randomized controlled trial. *Menopause*. 2012;19:749-759. <https://doi.org/10.1097/gme.0b013e31823fe835>
78. Fenlon D, Maishman T, Day L, et al. Effectiveness of nurse-led group CBT for hot flashes and night sweats in women with breast cancer: Results of the MENOS4 randomised controlled trial. *Psychooncology*. 2020;29(10):1514-1523. <https://doi.org/10.1002/pon.5432>
79. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol Off J Eur Soc Med Oncol*. 2020;31:1623-1649.
80. Wayne-Bossert P. Hypnosis for symptom management in adult cancer patients: what is the evidence? *Curr Treat Options Oncol*. 2024;25:364-375. <https://doi.org/10.1007/s11864-023-01168-y>
81. Carlson LE, Toivonen K, Flynn M, et al. The role of hypnosis in cancer care. *Curr Oncol Rep*. 2018;20:93. <https://doi.org/10.1007/s11912-018-0739-1>
82. Elkins GR, Fisher WI, Johnson AK, Carpenter JS, Keith TZ. Clinical hypnosis in the treatment of postmenopausal hot flashes: a randomized controlled trial. *Menopause*. 2013;20:291-298. <https://doi.org/10.1097/gme.0b013e31826ce3ed>
83. Elkins G, Marcus J, Stearns V, et al. Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors. *J Clin Oncol*. 2008;26:5022-5026. <https://doi.org/10.1200/JCO.2008.16.6389>
84. Piraccini E, Munakomi S, Chang K-V. Stellate Ganglion Blocks. In: *StatPearls*. StatPearls Publishing; 2023. Accessed October 16, 2023. Available at <http://www.ncbi.nlm.nih.gov/books/NBK507798/>
85. Goel V, Patwardhan AM, Ibrahim M, et al. Complications associated with stellate ganglion nerve block: a systematic review. *Reg*

- Anesth Pain Med.* 2019;44:669-678. <https://doi.org/10.1136/rapm-2018-100127>
86. Lee YS, Wie C, Pew S, Kling JM. Stellate ganglion block as a treatment for vasomotor symptoms: clinical application. *Cleve Clin J Med.* 2022;89:147-153. <https://doi.org/10.3949/ccjm.89a.21032>
 87. Walega DR, Rubin LH, Banuvar S, Shulman LP, Maki PM. Effects of stellate ganglion block on vasomotor symptoms: findings from a randomized controlled clinical trial in postmenopausal women. *Menopause.* 2014;21:807-814. <https://doi.org/10.1097/GME.0000000000000194>
 88. Van Hal M, Dydyk AM, Green MS. Acupuncture. In: *StatPearls*. StatPearls Publishing; 2023. Available at <http://www.ncbi.nlm.nih.gov/books/NBK532287/>. Accessed June 3, 2023.
 89. Lu W, Dean-Clover E, Doherty-Gilman A, Rosenthal DS. The value of acupuncture in cancer care. *Hematol Oncol Clin North Am.* 2008;22:631-648, viii. <https://doi.org/10.1016/j.hoc.2008.04.005>
 90. Avis NE, Coeytaux RR, Isom S, Prevette K, Morgan T. Acupuncture in Menopause (AIM) study: a pragmatic, randomized controlled trial. *Menopause.* 2016;23:626-637. <https://doi.org/10.1097/GME.0000000000000597>
 91. Lesi G, Razzini G, Musti MA, et al. Acupuncture as an integrative approach for the treatment of hot flashes in women with breast cancer: a prospective multicenter randomized controlled trial (AcCliMaT). *J Clin Oncol.* 2016;34:1795-1802. <https://doi.org/10.1200/JCO.2015.63.2893>
 92. Chiu H-Y, Pan C-H, Shyu Y-K, Han B-C, Tsai P-S. Effects of acupuncture on menopause-related symptoms and quality of life in women in natural menopause: a meta-analysis of randomized controlled trials. *Menopause.* 2015;22:234-244. <https://doi.org/10.1097/GME.0000000000000260>
 93. Avis NE, Coeytaux RR, Levine B, Isom S, Morgan T. Trajectories of response to acupuncture for menopausal vasomotor symptoms: the Acupuncture in Menopause study. *Menopause.* 2017;24:171-179. <https://doi.org/10.1097/GME.0000000000000735>
 94. Waldorff FB, Bang CW, Siersma V, Brodersen J, Lund KS. Factors associated with a clinically relevant reduction in menopausal symptoms of a standardized acupuncture approach for women with bothersome menopausal symptoms. *BMC Complement Med Ther.* 2021;21:29. <https://doi.org/10.1186/s12906-021-03208-2>
 95. Soares JM, Branco-de-Luca AC, da Fonseca AM, et al. Acupuncture ameliorated vasomotor symptoms during menopausal transition: single-blind, placebo-controlled, randomized trial to test treatment efficacy. *Menopause.* 2020;28:80-85. <https://doi.org/10.1097/GME.00000000000001651>
 96. Liljegen A, Gunnarsson P, Landgren B-M, et al. Reducing vasomotor symptoms with acupuncture in breast cancer patients treated with adjuvant tamoxifen: a randomized controlled trial. *Breast Cancer Res Treat.* 2012;135:791-798. <https://doi.org/10.1007/s10549-010-1283-3>
 97. Dodin S, Blanchet C, Marc I, et al. Acupuncture for menopausal hot flashes. *Cochrane Database Syst Rev.* 2013;2013:CD007410. <https://doi.org/10.1002/14651858.CD007410.pub2>
 98. McCarty MF. Isoflavones made simple - genistein's agonist activity for the beta-type estrogen receptor mediates their health benefits. *Med Hypotheses.* 2006;66:1093-1114. <https://doi.org/10.1016/j.mehy.2004.11.046>
 99. Velentzis LS, Woodside JV, Cantwell MM, Leathem AJ, Keshtgar MR. Do phytoestrogens reduce the risk of breast cancer and breast cancer recurrence? What clinicians need to know. *Eur J Cancer.* 2008;44:1799-1806. <https://doi.org/10.1016/j.ejca.2008.05.019>
 100. Franco OH, Chowdhury R, Troup J, et al. Use of plant-based therapies and menopausal symptoms: a systematic review and meta-analysis. *JAMA.* 2016;315:2554-2563. <https://doi.org/10.1001/jama.2016.8012>
 101. Lethaby A, Marjoribanks J, Kronenberg F, et al. Phytoestrogens for menopausal vasomotor symptoms. *Cochrane Database Syst Rev.* 2013;2013:CD001395. <https://doi.org/10.1002/14651858.CD001395.pub4>
 102. Dunneram Y, Chung H-F, Cade JE, et al. Soy intake and vasomotor menopausal symptoms among midlife women: a pooled analysis of five studies from the InterLACE consortium. *Eur J Clin Nutr.* 2019;73:1501-1511. <https://doi.org/10.1038/s41430-019-0398-9>
 103. Shike M, Doane AS, Russo L, et al. The effects of soy supplementation on gene expression in breast cancer: a randomized placebo-controlled study. *J Natl Cancer Inst.* 2014;106:dju189. <https://doi.org/10.1093/jnci/dju189>
 104. Becerra-Tomás N, Balducci K, Abar L, et al. Postdiagnosis dietary factors, supplement use and breast cancer prognosis: Global Cancer Update Programme (CUP Global) systematic literature review and meta-analysis. *Int J Cancer.* 2023;152:616-634. <https://doi.org/10.1002/ijc.34321>
 105. Ho SC, Yeo W, Goggins W, et al. Pre-diagnosis and early post-diagnosis dietary soy isoflavone intake and survival outcomes: a prospective cohort study of early stage breast cancer survivors. *Cancer Treat Res Commun.* 2021;27:100350. <https://doi.org/10.1016/j.ctarc.2021.100350>
 106. PDQ Integrative, Alternative, and Complementary Therapies Editorial Board. Black Cohosh (PDQ®): Health Professional Version. In: *PDQ Cancer Information Summaries*. National Cancer Institute (US); 2002. Available at <http://www.ncbi.nlm.nih.gov/books/NBK566616/>. Accessed June 3, 2023.
 107. Leach MJ, Moore V. Black cohosh (*Cimicifuga* spp.) for menopausal symptoms. *Cochrane Database Syst Rev.* 2012;2012:CD007244. <https://doi.org/10.1002/14651858.CD007244.pub2>
 108. Mahady GB, Low DT, Barrett ML, et al. United States pharmacopeia review of the black cohosh case reports of hepatotoxicity. *Menopause N Y N.* 2008;15:628-638.
 109. Fritz H, Seely D, McGowan J, et al. Black cohosh and breast cancer: a systematic review. *Integr Cancer Ther.* 2014;13:12-29. <https://doi.org/10.1177/1534735413477191>
 110. Trant AA, Chaggar A, Wei W, et al. The effect of black cohosh on Ki67 expression and tumor volume: a pilot study of ductal carcinoma in situ patients. *Integr Cancer Ther.* 2022;21:15347354221137290. <https://doi.org/10.1177/15347354221137290>
 111. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. *Ann Intern Med.* 1976;85:447-452. <https://doi.org/10.7326/0003-4819-85-4-447>
 112. MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flashes. *Cochrane Database Syst Rev.* 2004;2004:CD002978. <https://doi.org/10.1002/14651858.CD002978.pub2>
 113. Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321-333. <https://doi.org/10.1001/jama.288.3.321>
 114. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet Lond Engl.* 2019;394:1159-1168.
 115. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ.* 2019;364:l162.
 116. Committee on Gynecologic Practice. ACOG committee opinion no. 556: Postmenopausal estrogen therapy: route of administration and risk of venous thromboembolism. *Obstet Gynecol.* 2013;121:887-890.
 117. FDA Says Tibolone Not Approvable as a Menopause Treatment in the U.S. 2006. Available at https://www.drugs.com/nda/tibolone_060602.html. Accessed July 18, 2023.
 118. Kenemans P, Speroff L; International Tibolone Consensus Group. International tibolone consensus group. tibolone: clinical recommendations and practical guidelines. a report of the international

- tibolone consensus group. *Maturitas*. 2005;51:21-28. <https://doi.org/10.1016/j.maturitas.2005.02.011>
119. Formoso G, Perrone E, Maltoni S, et al. Short-term and long-term effects of tibolone in postmenopausal women. *Cochrane Database Syst Rev*. 2016;10:CD008536. <https://doi.org/10.1002/14651858.CD008536.pub3>
 120. Kenemans P, Bundred NJ, Foidart J-M, et al; LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *Lancet Oncol*. 2009;10:135-146. [https://doi.org/10.1016/S1470-2045\(08\)70341-3](https://doi.org/10.1016/S1470-2045(08)70341-3)
 121. The American College of Obstetricians and Gynecologists. Treatment of urogenital symptoms in individuals with a history of estrogen-dependent breast cancer: clinical consensus. *Obstet Gynecol*. 2021;138:950-960.
 122. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and management of testosterone deficiency: AUA Guideline. *J Urol*. 2018;200:423-432. <https://doi.org/10.1016/j.juro.2018.03.115>
 123. Quella SK, Loprinzi CL, Sloan JA, et al. Long term use of megestrol acetate by cancer survivors for the treatment of hot flashes. *Cancer*. 1998;82:1784-1788.
 124. Loprinzi CL, Levitt R, Barton D, et al. Phase III comparison of depomedroxyprogesterone acetate to venlafaxine for managing hot flashes: North Central Cancer Treatment Group Trial N99C7. *J Clin Oncol*. 2006;24:1409-1414. <https://doi.org/10.1200/JCO.2005.04.7324>
 125. Irani J, Salomon L, Oba R, Bouchard P, Mottet N. Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial. *Lancet Oncol*. 2010;11:147-154. [https://doi.org/10.1016/S1470-2045\(09\)70338-9](https://doi.org/10.1016/S1470-2045(09)70338-9)
 126. Holmberg L, Iversen O-E, Rudenstam CM, et al; HABITS Study Group. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J Natl Cancer Inst*. 2008;100:475-482. <https://doi.org/10.1093/jnci/djn058>
 127. Fahlén M, Fornander T, Johansson H, et al. Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial. *Eur J Cancer*. 2013;49:52-59. <https://doi.org/10.1016/j.ejca.2012.07.003>
 128. Wang Y, Lewin N, Qaoud Y, Rajaei AN, Scheer AS. The oncologic impact of hormone replacement therapy in premenopausal breast cancer survivors: a systematic review. *Breast*. 2018;40:123-130. <https://doi.org/10.1016/j.breast.2018.05.002>
 129. Mudhune GH, Armour M, McBride KA. Safety of menopausal hormone therapy in breast cancer survivors older than fifty at diagnosis: a systematic review and meta-analysis. *Breast*. 2019;47:43-55. <https://doi.org/10.1016/j.breast.2019.06.002>
 130. Poggio F, Del Mastro L, Bruzzone M, et al. Safety of systemic hormone replacement therapy in breast cancer survivors: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2022;191:269-275. <https://doi.org/10.1007/s10549-021-06436-9>
 131. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of clinical oncology breast cancer survivorship care guideline. *J Clin Oncol*. 2016;34:611-635. <https://doi.org/10.1200/JCO.2015.64.3809>
 132. Edey KA, Rundle S, Hickey M. Hormone replacement therapy for women previously treated for endometrial cancer. *Cochrane Database Syst Rev*. 2018;5:CD008830. <https://doi.org/10.1002/14651858.CD008830.pub3>
 133. Pergialiotis V, Pitsouni E, Prodromidou A, et al. Hormone therapy for ovarian cancer survivors: systematic review and meta-analysis. *Menopause*. 2016;23:335-342. <https://doi.org/10.1097/GME.0000000000000508>
 134. Achimaş-Cadariu PA, Păun DL, Paşca A. Impact of hormone replacement therapy on the overall survival and progression free survival of ovarian cancer patients: a systematic review and meta-analysis. *Cancers*. 2023;15:356. <https://doi.org/10.3390/cancers15020356>
 135. Valderrábano RJ, Pencina K, Storer TW, et al. Testosterone replacement in prostate cancer survivors with testosterone deficiency: study protocol of a randomized controlled trial. *Andrology*. 2023;11:93-102. <https://doi.org/10.1111/andr.13299>
 136. Loprinzi CL, Michalak JC, Quella SK, et al. Megestrol acetate for the prevention of hot flashes. *N Engl J Med*. 1994;331:347-352. <https://doi.org/10.1056/NEJM199408113310602>
 137. Sartor O, Eastham JA. Progressive prostate cancer associated with use of megestrol acetate administered for control of hot flashes. *South Med J*. 1999;92:415-416. <https://doi.org/10.1097/00007611-199904000-00013>
 138. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2018;103:1715-1744. <https://doi.org/10.1210/je.2018-00229>
 139. Salonia A, Bettocchi C, Capogrosso P, et al. EAU Guidelines on Sexual and Reproductive Health. 2024. Available at https://d56bochluxqzn.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Sexual-and-Reproductive-Health-2024_2024-05-23-101205_nmbi.pdf
 140. Kokorovic A, So AI, Serag H, et al. UPDATE - Canadian Urological Association guideline on androgen deprivation therapy: adverse events and management strategies. *Can Urol Assoc J*. 2022;16:E416-E431. <https://doi.org/10.5489/cuaj.8054>
 141. Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-pituitary and growth disorders in survivors of childhood cancer: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103:2761-2784. <https://doi.org/10.1210/je.2018-01175>
 142. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. *PLoS Med*. 2012;9:e1001275. <https://doi.org/10.1371/journal.pmed.1001275>
 143. Strongman H, Gadd S, Matthews A, et al. Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study using multiple linked UK electronic health records databases. *Lancet*. 2019;394:1041-1054. [https://doi.org/10.1016/S0140-6736\(19\)31674-5](https://doi.org/10.1016/S0140-6736(19)31674-5)
 144. Florido R, Daya NR, Ndumele CE, et al. Cardiovascular disease risk among cancer survivors: the Atherosclerosis Risk in Communities (ARIC) study. *J Am Coll Cardiol*. 2022;80:22-32. <https://doi.org/10.1016/j.jacc.2022.04.042>
 145. Travis LB, Hill D, Dores GM, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst*. 2005;97:1428-1437. <https://doi.org/10.1093/jnci/dji290>
 146. Masciari S, Dillon DA, Rath M, et al. Breast cancer phenotype in women with TP53 germline mutations: a Li-Fraumeni syndrome consortium effort. *Breast Cancer Res Treat*. 2012;133:1125-1130. <https://doi.org/10.1007/s10549-012-1993-9>
 147. Kuchenbaecker KB, Hopper JL, Barnes DR, et al; BRCA1 and BRCA2 Cohort Consortium. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA*. 2017;317:2402-2416. <https://doi.org/10.1001/jama.2017.7112>
 148. Kotsopoulos J, Gronwald J, Karlan BY, et al; Hereditary Breast Cancer Clinical Study Group. Hormone replacement therapy after oophorectomy and breast cancer risk among BRCA1 mutation carriers. *JAMA Oncol*. 2018;4:1059-1065. <https://doi.org/10.1001/jamaoncol.2018.0211>
 149. Huber D, Seitz S, Kast K, Emons G, Ortmann O. Hormone replacement therapy in BRCA mutation carriers and risk of ovarian, endometrial, and breast cancer: a systematic review. *J Cancer Res Clin Oncol*. 2021;147:2035-2045. <https://doi.org/10.1007/s00432-021-03629-z>
 150. National Cancer Institute. Breast Cancer Risk Assessment Tool: Online Calculator. Available at <https://bcrisktool.cancer.gov/>. Accessed July 18, 2023.
 151. Miyazaki K, Kaneko M, Narukawa M. Factors associated with high placebo response in clinical studies of hot flashes:

- a meta-analysis. *Menopause*. 2021;29:239-246. <https://doi.org/10.1097/GME.0000000000001895>
152. De Picker L, Van Den Eede F, Dumont G, Moorkens G, Sabbe BGC. Antidepressants and the risk of hyponatremia: a class-by-class review of literature. *Psychosomatics*. 2014;55:536-547. <https://doi.org/10.1016/j.psych.2014.01.010>
 153. Castillo JJ, Vincent M, Justice E. Diagnosis and management of hyponatremia in cancer patients. *Oncologist*. 2012;17:756-765. <https://doi.org/10.1634/theoncologist.2011-0400>
 154. Sanchez C, Reines EH, Montgomery SA. A comparative review of escitalopram, paroxetine, and sertraline: are they all alike? *Int Clin Psychopharmacol*. 2014;29:185-196. <https://doi.org/10.1097/YIC.0000000000000023>
 155. Kelly K, Posternak M, Alpert JE. Toward achieving optimal response: understanding and managing antidepressant side effects. *Dialogues Clin Neurosci*. 2008;10:409-418. <https://doi.org/10.31887/DCNS.2008.10.4/kelly>
 156. Stearns V, Johnson MD, Rae JM, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst*. 2003;95:1758-1764. <https://doi.org/10.1093/jnci/djg108>
 157. Zhong Z, Wang L, Wen X, et al. A meta-analysis of effects of selective serotonin reuptake inhibitors on blood pressure in depression treatment: outcomes from placebo and serotonin and noradrenaline reuptake inhibitor controlled trials. *Neuropsychiatr Dis Treat*. 2017;13:2781-2796. <https://doi.org/10.2147/NDT.S141832>
 158. Jacob S, Spinler SA. Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. *Ann Pharmacother*. 2006;40:1618-1622. <https://doi.org/10.1345/aph.1G293>
 159. Crépeau-Gendron G, Brown HK, Shorey C, et al. Association between citalopram, escitalopram and QTc prolongation in a real-world geriatric setting. *J Affect Disord*. 2019;250:341-345. <https://doi.org/10.1016/j.jad.2019.02.060>
 160. Gastaldon C, Schoretsanitis G, Arzenton E, et al. Withdrawal syndrome following discontinuation of 28 antidepressants: pharmacovigilance analysis of 31,688 reports from the WHO SPONTANEOUS REPORTING DATABASE. *Drug Saf*. 2022;45:1539-1549. <https://doi.org/10.1007/s40264-022-01246-4>
 161. Venlafaxine: Drug information. 2023. Available at <https://www.uptodate.com/>. Accessed June 3, 2023.
 162. McGeeney BE. Pharmacological management of neuropathic pain in older adults: an update on peripherally and centrally acting agents. *J Pain Symptom Manage*. 2009;38:S15-S27. <https://doi.org/10.1016/j.jpainsymman.2009.05.003>
 163. Golusinski LL, Blount BW. Clonidine-induced bradycardia. *J Fam Pract*. 1995;41:399-401.
 164. Sandweiss AJ, Morrison CM, Spichler A, Rozich J. A case report of clonidine induced syncope: a review of central actions of an old cardiovascular drug. *BMC Pharmacol Toxicol*. 2018;19:6. <https://doi.org/10.1186/s40360-018-0198-1>
 165. Clonidine: Drug information. 2023. Available at <https://www.uptodate.com/>. Accessed June 3, 2023.
 166. Tune LE. Anticholinergic effects of medication in elderly patients. *J Clin Psychiatry*. 2001;62:11-14.
 167. Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. *Lancet*. 2023;401:1091-1102. [https://doi.org/10.1016/S0140-6736\(23\)00085-5](https://doi.org/10.1016/S0140-6736(23)00085-5)
 168. US Food and Drug Administration. *FDA Adds Warning About Rare Occurrence of Serious Liver Injury with Use of Veozah (fezolinetant) for Hot Flashes Due to Menopause. Stop Medicine if Signs and Symptoms of Liver Injury Occur - Drug Safety Communication*. 2024. Available at <https://www.fda.gov/safety/medical-product-safety-information/fda-adds-warning-about-rare-occurrence-serious-liver-injury-use-veozah-fezolinetant-hot-flashes-due>. Accessed October 25, 2024.
 169. *Veozah (fezolinetant) [Prescribing Information]*. Astellas Pharma US, Inc; 2023. Available at https://www.astellas.com/us/system/files/veozah_uspi.pdf. Accessed February 23, 2024.
 170. Freeman EW, Guthrie KA, Caan B, et al. Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. *JAMA*. 2011;305:267-274. <https://doi.org/10.1001/jama.2010.2016>
 171. Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *JAMA*. 2003;289:2827-2834. <https://doi.org/10.1001/jama.289.21.2827>
 172. Stearns V, Slack R, Greep N, et al. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol*. 2005;23:6919-6930. <https://doi.org/10.1200/jco.2005.10.081>
 173. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet*. 2000;356:2059-2063. [https://doi.org/10.1016/S0140-6736\(00\)03403-6](https://doi.org/10.1016/S0140-6736(00)03403-6)
 174. Buijs C, Mom CH, Willemse PHB, et al. Venlafaxine versus clonidine for the treatment of hot flashes in breast cancer patients: a double-blind, randomized cross-over study. *Breast Cancer Res Treat*. 2009;115:573-580. <https://doi.org/10.1007/s10549-008-0138-7>
 175. Orleans RJ, Li L, Kim M-J, et al. FDA approval of paroxetine for menopausal hot flushes. *N Engl J Med*. 2014;370:1777-1779. <https://doi.org/10.1056/NEJMp1402080>
 176. Capriglione S, Plotti F, Montero R, et al. Role of paroxetine in the management of hot flashes in gynecological cancer survivors: results of the first randomized single-center controlled trial. *Gynecol Oncol*. 2016;143:584-588. <https://doi.org/10.1016/j.ygyno.2016.10.006>
 177. US Food and Drug Administration. *FDA Drug Safety Communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses*. 2012. Available at <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-revised-recommendations-celexa-citalopram-hydrobromide-related>. Accessed June 3, 2023.
 178. Beach SR, Celano CM, Sugrue AM, et al. QT prolongation, torsades de pointes, and psychotropic medications: a 5-year update. *Psychosomatics*. 2018;59(2):105-122. <https://doi.org/10.1016/j.psych.2017.10.009>
 179. Crandall CJ, Mehta JM, Manson JE. Management of menopausal symptoms: a review. *JAMA*. 2023;329:405-420. <https://doi.org/10.1001/jama.2022.24140>
 180. Higgins A, Nash M, Lynch AM. Antidepressant-associated sexual dysfunction: impact, effects, and treatment. *Drug Healthc Patient Saf*. 2010;2:141-150. <https://doi.org/10.2147/DHPS.S7634>
 181. Fava M. Weight gain and antidepressants. *J Clin Psychiatry*. 2000;61:37-41.
 182. Pandya KJ, Morrow GR, Roscoe JA, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet*. 2005;366:818-824. [https://doi.org/10.1016/S0140-6736\(05\)67215-7](https://doi.org/10.1016/S0140-6736(05)67215-7)
 183. Loprinzi CL, Qin R, Balcueva EP, et al. Phase III, randomized, double-blind, placebo-controlled evaluation of pregabalin for alleviating hot flashes, N07C1. *J Clin Oncol*. 2010;28:641-647. <https://doi.org/10.1200/JCO.2009.24.5647>
 184. Lavigne JE, Heckler C, Mathews JL, et al. A randomized, controlled, double-blinded clinical trial of gabapentin 300 versus 900 mg versus placebo for anxiety symptoms in breast cancer survivors. *Breast Cancer Res Treat*. 2012;136:479-486. <https://doi.org/10.1007/s10549-012-2251-x>
 185. Domecq JP, Prutsky G, Leppin A, et al. Clinical review: drugs commonly associated with weight change: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2015;100:363-370. <https://doi.org/10.1210/jc.2014-3421>

186. Laufer LR, Erlik Y, Meldrum DR, Judd HL. Effect of clonidine on hot flashes in postmenopausal women. *Obstet Gynecol.* 1982;60:583-586.
187. Nagamani M, Kelter ME, Smith ER. Treatment of menopausal hot flashes with transdermal administration of clonidine. *Am J Obstet Gynecol.* 1987;156:561-565. [https://doi.org/10.1016/0002-9378\(87\)90050-0](https://doi.org/10.1016/0002-9378(87)90050-0)
188. Goldberg RM, Loprinzi CL, O'Fallon JR, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *J Clin Oncol.* 1994;12:155-158. <https://doi.org/10.1200/JCO.1994.12.1.155>
189. Pandya KJ, Raubertas RF, Flynn PJ, et al. Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. *Ann Intern Med.* 2000;132:788-793. <https://doi.org/10.7326/0003-4819-132-10-200005160-00004>
190. Boekhout AH, Vincent AD, Dalesio OB, et al. Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol.* 2011;29:3862-3868. <https://doi.org/10.1200/JCO.2010.33.1298>
191. Leon-Ferre RA, Novotny PJ, Wolfe EG, et al. Oxybutynin vs placebo for hot flashes in women with or without breast cancer: a randomized, double-blind clinical trial (ACCRU SC-1603). *JNCI Cancer Spectr.* 2020;4:pkz088. <https://doi.org/10.1093/jncics/pkz088>
192. Welk B, Etaby K, McArthur E, Chou Q. The risk of delirium and falls or fractures with the use of overactive bladder anticholinergic medications. *Neurol Urodyn.* 2022;41:348-356. <https://doi.org/10.1002/nau.24827>
193. Simon JA, Gaines T, LaGuardia KD. Extended-release oxybutynin therapy for vasomotor symptoms in women: a randomized clinical trial. *Menopause N Y N.* 2016;23:1214-1221. <https://doi.org/10.1097/gme.0000000000000773>
194. FDA Approves Novel Drug to Treat Moderate to Severe Hot Flashes Caused by Menopause. 2023. Available at <https://www.fda.gov/news-events/press-announcements/fda-approves-novel-drug-treat-moderate-severe-hot-flashes-caused-menopause>. Accessed February 23, 2024.
195. Morga A, Ajmera M, Gao E, et al. Systematic review and network meta-analysis comparing the efficacy of fezolinetant with hormone and nonhormone therapies for treatment of vasomotor symptoms due to menopause. *Menopause.* 2024;31:68-76. <https://doi.org/10.1097/GME.0000000000002281>
196. Santoro N, Nappi RE, Neal-Perry G, et al. Fezolinetant treatment of moderate-to-severe vasomotor symptoms due to menopause: effect of intrinsic and extrinsic factors in two phase 3 studies (SKYLIGHT 1 and 2). *Menopause.* 2024;31:247-257. <https://doi.org/10.1097/GME.0000000000002340>
197. Neal-Perry G, Cano A, Lederman S, et al. Safety of fezolinetant for vasomotor symptoms associated with menopause: a randomized controlled trial. *Obstet Gynecol.* 2023;141:737-747. <https://doi.org/10.1097/AOG.0000000000005114>
198. Johnson KA, Martin N, Nappi RE, et al. Efficacy and safety of fezolinetant in moderate to severe vasomotor symptoms associated with menopause: a phase 3 RCT. *J Clin Endocrinol Metab.* 2023;108:1981-1997. <https://doi.org/10.1210/clinem/dgad058>
199. Simon JA, Anderson RA, Ballantyne E, et al. Efficacy and safety of elinzanetant, a selective neurokinin-1,3 receptor antagonist for vasomotor symptoms: a dose-finding clinical trial (SWITCH-1). *Menopause.* 2023;30:239-246. <https://doi.org/10.1097/GME.0000000000002138>
200. Vrselja A, Latifi A, Baber RJ, et al. Q-122 as a novel, non-hormonal, oral treatment for vasomotor symptoms in women taking tamoxifen or an aromatase inhibitor after breast cancer: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet.* 2022;400:1704-1711. [https://doi.org/10.1016/S0140-6736\(22\)01977-8](https://doi.org/10.1016/S0140-6736(22)01977-8)