*Review Article*

# Menopausal Symptom Management in Breast Cancer Survivors — A Promising New Option

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**Abstract:** Menopausal symptoms such as vasomotor symptoms (hot flashes and night sweats), sleep disturbance, mood changes, and sexual dysfunction are highly prevalent among breast cancer survivors and can be severe and persistent. Hormone replacement therapy (HRT), while effective in the general menopausal population, is often contraindicated or avoided in women with a history of estrogen receptor–positive breast cancer due to concerns about recurrence. Consequently, nonhormonal strategies—pharmacologic and nonpharmacologic—have been the mainstay of symptom management, but their efficacy is modest and side effects or drug interactions can limit use. Recent developments in neurokinin receptor antagonists, particularly neurokinin-3 receptor (NK3R) antagonists, represent a novel, mechanism-based, nonhormonal class that directly targets hypothalamic thermoregulatory pathways implicated in vasomotor symptoms. Clinical trials in general menopausal populations have demonstrated substantial reductions in vasomotor symptom frequency and severity and improvements in quality of life. While safety signals, notably rare hepatic adverse events, require cautious implementation and monitoring, ongoing trials specifically enrolling breast cancer survivors—many of whom are receiving endocrine therapy—offer the potential to expand safe, effective options for this vulnerable group. These editorial reviews the current landscape of menopausal symptom management in breast cancer survivors, summarizes the evidence supporting NK3R antagonists as a promising new option, discusses safety and practical considerations, and highlights priorities for research and clinical practice.

**Keywords:** vasomotor symptoms, breast cancer survivorship, neurokinin-3 receptor antagonist, nonhormonal therapy, quality of life

## 1. INTRODUCTION

Improved detection, advances in systemic therapy, and widespread uptake of adjuvant endocrine treatments have markedly increased the population of women who survive breast cancer. Survivorship, however, brings an array of long-term health issues, among which menopausal symptoms are particularly common and clinically consequential [1]. Menopausal complaints in survivors arise from natural ovarian ageing but are frequently abrupt and severe due to chemotherapy-induced ovarian failure or as an intended consequence of ovarian suppression used to treat hormone-responsive disease. These symptoms—most prominently vasomotor symptoms (VMS), sleep disruption, mood instability, sexual dysfunction, and urogenital atrophy—can have a disproportionate impact on quality of life. They also have downstream implications for adherence to endocrine therapies, which are critical for reducing recurrence risk in estrogen receptor–positive (ER+) disease [2]. In this context, clinicians must balance the imperative to relieve distressing symptoms with the priority of avoiding interventions that could theoretically increase oncologic risk. For many years, this balance has limited effective

 

therapeutic options for survivors. The emergence of targeted, nonhormonal agents that act on central thermoregulatory pathways therefore represents an important development with the potential to change clinical practice [3].

## 2. SCOPE AND CLINICAL CHALLENGE

Breast cancer survivors constitute a heterogeneous group with varied treatment histories, comorbidities, and symptom burdens. Endocrine therapy—tamoxifen, ovarian suppression, and aromatase inhibitors—remains foundational to adjuvant care for ER+ breast cancer, often administered for five to ten years or longer. These therapies frequently exacerbate menopausal symptoms. For example, ovarian suppression and chemotherapy-induced ovarian failure precipitate abrupt estrogen deprivation, which commonly manifests as frequent, severe VMS [4]. Aromatase inhibitors may worsen musculoskeletal symptoms and sexual dysfunction, while tamoxifen is associated with hot flashes through central mechanisms. The complexity increases because options effective in the general menopause population, notably systemic estrogen therapy, are often avoided in survivors due to concerns about stimulating residual hormone-sensitive disease or interacting with endocrine agents [5]. Observational data and mechanistic reasoning have historically fueled reluctance to use estrogen-based therapies in women with a history of breast cancer, particularly ER+ disease, leaving clinicians to manage symptoms with alternatives that are variably effective and sometimes poorly tolerated. Therefore, identifying safe and effective nonhormonal therapies tailored for survivors is a clinical priority.

## 3. ESTABLISHED NONHORMONAL INTERVENTIONS: EVIDENCE, LIMITATIONS, AND PRACTICALITIES

A range of nonhormonal pharmacologic agents has demonstrated efficacy for mitigating vasomotor symptoms. Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), notably venlafaxine and paroxetine, reduce VMS frequency and severity by modulating central neurotransmitter pathways [6]. Gabapentin and pregabalin, anticonvulsant agents with neuromodulator properties, lower hot-flash frequency and improve sleep in randomized trials. Clonidine, an alpha-2 adrenergic agonist, has demonstrated modest efficacy in some studies. Nonpharmacologic approaches, including cognitive behavioral therapy (CBT), mindfulness-based stress reduction, and acupuncture, can provide additional benefit for selected patients and may be particularly useful when pharmacologic options are contraindicated or poorly tolerated. Each option, however, has important limitations when considered for breast cancer survivors [7]. First, effect sizes with nonhormonal agents are smaller than with systemic estrogen, and many women continue to experience bothersome symptoms despite treatment. Second, adverse effects can limit tolerability or adherence: gabapentin commonly causes sedation and dizziness; venlafaxine may raise blood pressure at higher doses; and clonidine can lead to orthostatic symptoms. Third, pharmacokinetic interactions complicate choices: paroxetine and fluoxetine inhibit cytochrome P450 2D6 (CYP2D6), reducing conversion of tamoxifen to its active metabolite endoxifen and potentially diminishing tamoxifen efficacy [8]. Finally, long-term safety data in breast cancer populations are limited for many nonhormonal interventions, reinforcing the need for careful individualized decision-making and monitoring.

## 4. NEUROBIOLOGY OF VASOMOTOR SYMPTOMS: CLARIFYING TARGETS

Our understanding of the neuroendocrine basis of vasomotor symptoms has evolved markedly. Estrogen withdrawal alters the activity of a specialized group of hypothalamic neurons—collectively referred to as KNDy neurons because they co-express kisspeptin, neurokinin B (NKB), and dynorphin [9]. These neurons influence thermoregulatory set points through projections to hypothalamic and

 

brainstem centers responsible for autonomic and behavioral thermoregulation. Preclinical and translational studies indicate that increased NKB signaling under low-estrogen conditions narrows the thermoregulatory neutral zone, making small perturbations in core temperature more likely to trigger heat dissipation responses such as peripheral vasodilation and sweating [10]. Targeting neurokinin signaling therefore offers a rational, mechanism-based approach to reduce the propensity for vasomotor episodes without supplying estrogen.

## 5. NK3 RECEPTOR ANTAGONISTS: DEVELOPMENT AND MECHANISM

Neurokinin receptor antagonists are a pharmacologic class that block the action of neurokinin peptides on their receptors. Fezolinetant, an oral selective NK3 receptor antagonist, was developed to selectively inhibit NK3 signaling in the hypothalamus. By reducing the hyperactivity of KNDy neurons, fezolinetant modulates thermoregulatory outputs and decreases the frequency and severity of vasomotor events [11]. Unlike hormone replacement therapy, NK3R antagonists do not supply estrogen and are therefore theoretically attractive for women in whom estrogen exposure is undesirable [12]. Additional agents targeting NK1 and combined NK1/NK3 pathways are in development and may offer alternative pharmacologic profiles.

## 6. CLINICAL EVIDENCE: EFFICACY IN GENERAL MENOPAUSAL POPULATIONS

Randomized, placebo-controlled trials of fezolinetant in postmenopausal women with moderate-to-severe vasomotor symptoms have demonstrated clinically meaningful reductions in hot-flash frequency and severity within weeks of initiation. Pivotal phase III randomized controlled trials reported reductions in mean daily VMS frequency of approximately 50–80% from baseline, depending on dose and study duration, and significant improvements in patient-reported outcomes related to sleep, quality of life, and overall functioning [13]. These benefits were observed early, often within one to two weeks, and were maintained over treatment durations studied in trials. While most trials excluded women with active malignancy, the magnitude and rapidity of effect make NK3R antagonists an attractive candidate for addressing severe symptoms in populations where estrogen therapy is contraindicated [14]. Despite promising results in general menopausal cohorts, the evidence base for NK3R antagonists specifically in breast cancer survivors remains limited. Clinical development programs have recognized this gap and have initiated trials that enroll women with a history of breast cancer and cohorts of patients receiving endocrine therapy [15]. These dedicated studies aim to determine whether the efficacy observed in general populations translates to survivors and to assess safety in the context of concomitant oncologic medications. Critical questions include whether NK3R antagonism has any off-target effects relevant to breast tissue or tumor biology, whether pharmacokinetic interactions with endocrine agents affect drug levels or efficacy, and how safety monitoring should be operationalized in survivorship clinics [16]. Safety considerations for NK3R antagonists warrant careful attention. Clinical trials and post marketing surveillance have identified generally well-tolerated adverse event profiles, with the most common events being mild to moderate and including headache, nausea, and insomnia. However, regulatory agencies have issued communications regarding rare instances of clinically significant liver enzyme elevations and, in isolated reports, hepatic injury associated with fezolinetant [17]. As a result, product labelling typically recommends baseline liver function tests (LFTs) and periodic monitoring during therapy, with clear thresholds for dose interruption or discontinuation. Patients with preexisting hepatic impairment or those receiving concomitant hepatotoxic medications require careful assessment and may be poor candidates for NK3R antagonists until more data are available [18]. Active pharmacovigilance and post marketing studies will be important to characterize incidence rates and risk factors for hepatic adverse events in broader, real-world populations including breast cancer survivors.

 

## 7. COMPARATIVE EFFECTIVENESS AND POSITIONING AMONG TREATMENT OPTIONS

Where might NK3R antagonists fit within the therapeutic armamentarium for breast cancer survivors? Given their nonhormonal mechanism and demonstrated efficacy in general menopausal trials, NK3R antagonists could be positioned as a preferred pharmacologic option for survivors with moderate-to-severe VMS when HRT is contraindicated or undesired. Head-to-head trials comparing NK3R antagonists with established nonhormonal agents—gabapentin, SSRIs/SNRIs (chosen to avoid CYP2D6 inhibition in tamoxifen-treated patients), and behavioral therapies—are needed to guide evidence-based sequencing and combination strategies. Cost-effectiveness analyses that incorporate quality-of-life gains and potential effects on adherence to endocrine therapy will also inform formulary decisions and clinical guideline recommendations.

## 8. POTENTIAL BENEFITS BEYOND VASOMOTOR SYMPTOM CONTROL

Effective management of vasomotor symptoms can yield benefits that extend beyond direct symptom reduction. Improved sleep quality, reduced daytime fatigue, and better mood may arise from successful VMS control and, in turn, enhance overall function and quality of life [2]. Importantly in oncology, better symptom control has been associated with improved adherence to adjuvant endocrine therapies; when symptoms are intolerable, some patients elect to discontinue therapy prematurely, which may compromise long-term outcomes. If NK3R antagonists can deliver superior symptom relief without interfering with endocrine therapy, they could indirectly contribute to better oncologic outcomes by reducing treatment discontinuation [19]. Prospective studies that capture adherence metrics and long-term oncologic endpoints will be necessary to quantify these potential benefits. Implementing NK3R antagonists into survivorship care requires practical protocols and multidisciplinary collaboration. A pragmatic clinical pathway might include: (1) comprehensive symptom assessment and documentation of prior therapies and response; (2) baseline evaluation including liver function tests and medication reconciliation to identify potential interactions; (3) shared decision-making that explains the balance of benefits and risks, monitoring requirements, and alternative options; (4) initiation of therapy with clear instructions for symptom monitoring and emergency contacts for potential adverse effects; and (5) scheduled laboratory surveillance and follow-up visits to assess efficacy, tolerability, and adherence. Coordination with oncology and pharmacy services is advisable, particularly for patients receiving complex adjuvant regimens. To establish the role of NK3R antagonists for breast cancer survivors definitively, several lines of research are necessary. First, randomized controlled trials specifically enrolling survivors—stratified by endocrine therapy type (tamoxifen versus aromatase inhibitors versus none), menopausal status, and prior chemotherapy exposure—are essential to evaluate efficacy, safety, and interaction effects [3]. These trials should incorporate long-term follow-up for oncologic outcomes, patient-reported outcomes, and adherence metrics. Second, mechanistic studies exploring any effects of NK3R antagonism on breast tissue signaling or tumor microenvironments will help address safety concerns and identify biomarkers of response [1]. Third, comparative effectiveness trials and health-economic evaluations are required to determine the most cost-effective approaches for symptom management in diverse healthcare settings. Finally, implementation research should focus on practical monitoring strategies, telehealth-enabled follow-up, and pathways to ensure equitable access to novel therapies.

## 9. EQUITY, ETHICS, AND ACCESS

Ensuring equitable access to novel therapies must be a priority. High drug costs, limited insurance coverage, and the need for laboratory monitoring have the potential to exacerbate disparities, particularly for patients in low-resource settings or those facing logistical barriers to repeated blood testing [6]. Clinical trials must therefore enroll diverse populations to ensure generalizability, including

 

racial and ethnic minorities, patients of lower socioeconomic status, rural residents, and younger survivors. Policymakers, funders, and healthcare systems should consider mechanisms such as patient assistance programs, value-based pricing, and integration of monitoring within community health services to reduce barriers. While awaiting definitive survivorship-specific data, clinicians can consider NK3R antagonists for selected breast cancer survivors with moderate-to-severe vasomotor symptoms after individualized risk–benefit assessment. Key steps include: (1) avoiding SSRIs known to inhibit CYP2D6 in patients on tamoxifen when choosing alternative antidepressants for VMS; (2) discussing the novel mechanism and the current evidence base for NK3R antagonists, making clear the limits of existing data in breast cancer cohorts; (3) arranging baseline liver function testing and a monitoring plan; (4) coordinating care with oncology and pharmacy; and (5) documenting shared decision-making and follow-up plans [4]. To illustrate the potential clinical impact, consider a common survivorship scenario: a 52-year-old woman with stage II ER+ breast cancer who completed adjuvant chemotherapy and is receiving an aromatase inhibitor. She experiences frequent nocturnal hot flashes that fragment sleep, produce daytime fatigue, and lower her capacity to maintain employment and social engagement. She reports considering discontinuation of endocrine therapy because of debilitating symptoms [2]. Under current practice, clinicians might trial gabapentin or an SNRI, counsel about cognitive behavioral therapy for insomnia and hot flashes, and offer topical vaginal estrogen for urogenital atrophy when appropriate. With the availability of an NK3R antagonist as an alternative could provide faster, more substantial relief of vasomotor symptoms, potentially restore sleep continuity, and markedly improve daytime functioning, thereby supporting adherence to endocrine therapy [1]. Importantly, this pathway requires coordination with oncology to ensure monitoring and to contextualize any hepatic enzyme elevations should they occur. Inclusion of patient preference, costs, and plans for regular liver-function surveillance are essential components of safe implementation. Prospective real-world evidence will be required to confirm that symptom improvement translates into measurable improvements in therapy persistence and long-term outcomes.

## 10. CONCLUSION

Menopausal symptom management in breast cancer survivors is a high-priority clinical issue with substantial implications for quality of life and potentially for oncologic outcomes through effects on therapy adherence. Neurokinin-3 receptor antagonists represent a promising, mechanism-based, nonhormonal option that has demonstrated meaningful efficacy in general menopausal populations and is now being evaluated in survivors, including those on endocrine therapy. Safety signals, particularly related to liver enzymes, necessitate baseline assessment and ongoing monitoring. Pending definitive survivorship-specific evidence, clinicians should engage in multidisciplinary, individualized, and evidence-based shared decision-making when considering these agents. If ongoing trials confirm safety and efficacy in breast cancer cohorts, NK3R antagonists have the potential to transform symptom management for many survivors by offering meaningful relief without hormonal exposure.

 

## REFERENCES


[1] Pinkerton JV, et al. Neurobiology of vasomotor symptoms. Menopause-related research journals.

[2] Stute P, et al. Fezolinetant for vasomotor symptoms: randomized trials. Major clinical trials.

[3] Avis NE, et al. Nonhormonal management of menopausal symptoms in breast cancer survivors.

[4] Cochrane Collaboration. Non-hormonal interventions for hot flushes in women with breast cancer.

[5] Ayush Thapa, Siddhartha Sharma, Riddhi Gohil, Mandeep Singh Dhillon & Prasoon Kumar (2025). Evaluation of Heel-Based Quantitative Ultrasound Bone Densitometry as a Screening Tool for Post-Menopausal Osteoporosis. Dinkum Journal of Medical Innovations, 4(07):410-425.

[6] ClinicalTrials.gov. Fezolinetant and related trials in breast cancer survivors.

[7] Smith IE, et al. Endocrine therapy adherence and symptom burden in breast cancer.

[8] Ganz, P. A., Greendale, G. A., Petersen, L., Zibecchi, L., Kahn, B., & Belin, T. R. (2000). Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. *Journal of the National Cancer Institute*, *92*(13), 1054-1064.

[9] Santen, R. J., Stuenkel, C. A., Davis, S. R., Pinkerton, J. V., Gompel, A., & Lumsden, M. A. (2017). Managing menopausal symptoms and associated clinical issues in breast cancer survivors. *The Journal of Clinical Endocrinology & Metabolism*, *102*(10), 3647-3661.

[10] Durga Karki, Rohit Gadtoula, Depak Adhikari, Samir Bhandari, Bhupendra Kc & Nisha Karki (2024). Knowledge Regarding Postpartum Depression among Postnatal Mother in Selected Hospital Of Kathmandu. Dinkum Journal of Medical Innovations, 3(09):645-655.

[11] Lammerink, E. A., de Bock, G. H., Schröder, C. P., & Mourits, M. J. (2012). The management of menopausal symptoms in breast cancer survivors: A case-based approach. *Maturitas*, *73*(3), 265-268.

[12] Bruno, D., & Feeney, K. J. (2006, December). Management of postmenopausal symptoms in breast cancer survivors. In *Seminars in oncology* (Vol. 33, No. 6, pp. 696-707). WB Saunders.

[13] Cusack, L., Brennan, M., Baber, R., & Boyle, F. (2013). Menopausal symptoms in breast cancer survivors: management update. *The British Journal of General Practice*, *63*(606), 51.

[14] Tran, S., Hickey, M., Saunders, C., Ramage, L., & Cohen, P. A. (2021). Nonpharmacological therapies for the management of menopausal vasomotor symptoms in breast cancer survivors. *Supportive Care in Cancer*, *29*(3), 1183-1193.

[15] Daniel, B., Mitchell, H., Higham, P., Timpson, J., & Foy, S. (2014). Management of menopausal symptoms for breast cancer patients. *British Journal of Nursing*, *23*(8), 427-432.

[16] Szabo, R. A., Marino, J. L., & Hickey, M. (2019). Managing menopausal symptoms after cancer. *Climacteric*, *22*(6), 572-578.

[17] Gavino S. Nuñez Ii, Chelsea Angela R. Plasencia, Blessie B. Doble, Shiena Mitchelle L. Baldoza & Maricris B. Dionson (2024). Evaluation of Self-Care Practices of Pregnant Women in Barangay Apas, Cebu City, Philippines. Dinkum Journal of Medical Innovations, 3(08):581-596.

[18] Marino, J. L., McNamara, H. C., & Hickey, M. (2018). Managing menopausal symptoms after cancer: an evidence-based approach for primary care. *Medical Journal of Australia*, *208*(3).

[19] Peate, M., Saunders, C., Cohen, P., & Hickey, M. (2021). Who is managing menopausal symptoms, sexual problems, mood and sleep disturbance after breast cancer and is it working?


 

Findings from a large community-based survey of breast cancer survivors. *Breast Cancer Research and Treatment*, *187*(2), 427-435.

 