THERAPEUTIC ADVANCES in
Reproductive Health

Review

Neurokinin receptor antagonists as potential non-hormonal treatments for vasomotor symptoms of menopause

Ther Adv Reprod Health

2023, Vol. 17: 1–8

DOI: 10.1177/26334941231177611

Melissa Conklin and Nanette Santoro

***Abstract*:** Vasomotor symptoms of menopause (VMS), otherwise known as hot flashes, can significantly impact women's quality of life. Up to 87% of women report hot flashes during or after their menopause transition, and can last for a median duration of 7.4 years. The current mainstay of treatment and the most effective treatment for VMS is hormone therapy with estrogen. However, hormone therapy is not without risk, and the discovery of an effective nonhormonal treatment option with neurokinin B receptor antagonists for VMS provides an encouraging and potentially practice-changing treatment option for all women. This review will discuss the pathophysiology and mechanism of action, as well as review the current compounds in development targeting the neurokinin receptors.

Keywords: hot flashes, KNDy neurons, menopause, neurokinin receptor, vasomotor symptoms

Received: 1 June 2022; revised manuscript accepted: 5 May 2023.

Correspondence to:
Nanette Santoro
Department of Obstetrics and Gynecology, University of Colorado School of Medicine, 12631 E 17th Avenue, Academic Office-1 Room 4004, Aurora, CO 80045, USA
Nanette.santoro@cuanschutz.edu

Melissa Conklin
Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora, CO, USA

Introduction

Menopause is the permanent cessation of menstruation that occurs after loss of ovarian activity, degeneration of ovarian follicles, and loss of ovarian estrogen secretion. It is a normal and expected transitional life occurrence. Clinical manifestations include genitourinary symptoms, sleep disturbances, mood changes, decreased libido, joint pain, and vasomotor symptoms (VMSs), otherwise known as hot flashes. Hot flashes are typically short, sudden sensations of heat in the upper body, often characterized by perspiration, flushing, chills, clamminess, anxiety, and heart palpitations. These symptoms can be disruptive and bothersome to women, as up to 87% of women report hot flashes during or after their menopause transition.[1] This review first addresses the impact of VMSs on women's lives and traditional treatments and then focuses on the newest advances in pathophysiology that have led to targeting of the neurokinin-3 receptor (NK3R) for the alleviation of this cardinal symptom of menopause.

Search strategy for the review

Because the field is in its infancy, there are few published clinical trials and many agents in development. Our search strategy primarily utilized PubMed to identify publications that included human research and clinical trials as well as the keywords NK3R, hot flashes, and VMSs. Additional searches of clinicaltrials.gov using the keywords hot flashes and VMSs were performed to identify unpublished data, and abstracts from national and international menopause and other scientific meetings were searched for specific compounds.

The impact and pathophysiology of menopausal VMSs

Symptoms of menopause can significantly impact women's quality of life. A large US population-based study by Williams *et al.* found that hot flashes cause a substantial burden on women's lives. They found that VMSs interfered with work, social activities, leisure activities, and sexual activity. VMS also impacted sleep, mood, concentration, total energy level, and overall quality of life.[2] Lost productivity due to interference at work includes significantly increased time missed from work, as well as impairment at work.[3] In addition, social factors and lifestyle choices

contribute to the impact of menopausal symptoms on quality of life. Smoking was shown to increase the risk of hot flashes, while being younger at time of symptom onset, lack of physical activity and having a higher BMI resulted in poorer quality of life in relation to menopausal symptoms.[2] While it has been shown that VMS leads to significantly decreased quality of life, Avis *et al.*[4] found the median total duration to be 7.4 years, with African-American women experiencing VMS for a medial duration of 10.1 years. They found the single most powerful predictor of total duration of VMS to be age at which women first experienced VMS. Together, these studies found that women who experienced onset of VMS at a younger age were shown to have significantly longer total duration, as well as decreased quality of life.[2,4]

While the pathophysiology of VMS is not completely understood, their onset is thought to be related to the narrowing of the thermoregulatory system, which maintains the core body temperature within the thermoregulatory zone. The decline in estrogen can be due to the physiologic menopausal transition, anti-estrogenic medications or gonadectomy. Decreased estrogen results in an apparent narrowing of the comfortable temperature range for an individual, which causes the perception of excessive warmth to occur at temperatures at which the individual would have previously been comfortable or thermoneutral.[5] Women undergoing the menopausal transition are more likely to experience symptoms, such as hot flashes, with changes in the core body temperature outside of the thermoregulatory zone as the thermoregulatory zone is narrowed in menopause.[6] Autonomic thermoeffector pathways in the median pre-optic nucleus responds to fluctuations in body temperature outside of the thermoregulatory zone, which subsequently leads to cutaneous vasodilatation, which is the hallmark of VMS.[7] Despite the association of VMS with the decline in estradiol associated with menopause, ambient estradiol levels during a hot flash, particularly in perimenopausal women, do not always predict VMS. There is likely some relationship to dynamic changes in estradiol during the menopause transition and early postmenopausal that precipitate VMS and some studies have associated VMS with more variable estradiol levels in perimenopausal women. The fact that most women restabilize at some time point after menopause and stop experiencing VMS indicates that low estradiol levels alone may not be sufficient to trigger VMS and that other mechanisms are at play. Estrogen plays an important role in body temperature regulation, as it has been clearly shown that treatment with estrogen improves VMS.

Discovery of the role of the NK3R in VMS pathophysiology

The hypothalamic-pituitary ovarian axis is responsible for reproductive function in women. Gonadotropin releasing hormone (GnRH) is released in a pulsatile fashion from the hypothalamus, which in turn triggers the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. Elevated FSH and LH trigger the release of estrogen from the ovaries, which then leads to a negative feedback effect on the secretion of GnRH. Postmortem studies performed by Rance *et al.*[8] found hypertrophy of a subpopulation of neurons in the arcuate nucleus, called the "KNDy neurons," in postmenopausal women. These estrogen-responsive neurons express kisspeptin, neurokinin B (NKB), and dynorphin, which have been found to be implicated in the secretion of GnRH.[9] The NKB and dynorphin neurons act on the kisspeptin neurons to stimulate the secretion of kisspeptin. In turn, the kisspeptin drives the secretion of GnRH in a pulsatile fashion. Elevated circulating levels of estrogen suppress kisspeptin and the expression of the KNDy neurons, which in turn leads to reduced secretion of GnRH and LH.[10] In addition, these neurons have projection pathways to the warmth-sensing neurons in the medial preoptic area of the brain, so it is thought that NKB signaling could additionally influence heat-defense effectors and cutaneous vasodilatation.[8] In summary, estrogen deficiency in menopause leads to the upregulation of NKB and its receptor (NK3R) via the median preoptic nucleus, which receives input and projects to the autonomic thermoregulatory pathway leading to the hallmark symptom of cutaneous vasodilatation, VMS.[11]

In 2017, Crandall *et al.* performed a genome-wide association study to evaluate the relationship of genetic variation and VMSs of menopause. In this study, they found that the tachykinin receptor 3 gene on chromosome 14 was associated with VMSs.[12] The tachykinin receptor 3 (TAC3R) gene encodes for NKB receptor, thus supporting a biological pathway involved in

VMSs. Mittleman-Smith *et al.* ablated the KNDy neurons in ovariectomized rats with a selective toxin and compared skin-tail vasodilation to ovariectomized rats with intact KNDy neurons. They found that the average core temperature of the ovariectomized control rats was significantly elevated compared to the ovariectomized rats with ablated KNDy neurons, suggesting that blocking the KNDy neuroendocrine pathway is associated with improved VMSs.[7]

Other molecular targets currently being studied for nonhormonal treatments of menopause discussed in this review include the transient receptor potential melastatin 8 channel (TRPM8) channel, chemokine receptor type 4 (CXCR4) receptor, and granulocyte colony-stimulating factor. TRPM8 plays a role in the sensation of cold temperature, and it is hypothesized that a TRPM8 antagonist would reduce VMSs by using the body's natural cooling to prevent increases in core body temperature leading to improvement in VMSs.[13] CXCR4 interacts with the KNDy neurons as described above and could be utilized as a target for treatment options.

Traditional treatments for VMSs

The current mainstay of treatment for VMSs of menopause is hormone therapy and it remains the most effective treatment. Systemic hormone therapy with estrogen alone or in combination with progestin is the most effective treatment for VMS.[1] In users of oral estrogen or oral estrogen plus progestin compared to placebo showed a 75% reduction in weekly hot flush frequency.[1] Estrogen can be administered orally or transdermally via patches, gels or sprays. However, hormone therapy is not without risk. The Women's Health Initiative study found that hormonal therapy with estrogen plus progestin was associated with an increased risk of breast cancer and cardiovascular disease, including coronary heart disease, stroke, and thromboembolic disease.[14] The effect of hormone therapy on the risk of coronary heart disease was found to be associated with age. A meta-analysis in 2006, including the WHI study and 22 smaller studies, found that hormone therapy reduced coronary heart disease events in younger postmenopausal women, those aged less than 60 years of age, and those less than 10 years from menopause onset.[15] For women who had had a hysterectomy, hormone therapy with estrogen only was associated with fewer risks—importantly, breast cancer risk was not increased with this treatment—but did not have sufficient long-term benefit to justify its use in the absence of symptoms. Thus, the American College of Obstetricians and Gynecologists recommends individualizing hormone treatment based on each woman's risk–benefit ratio and their clinical symptoms.[1]

Given the risks of hormone treatment for VMS, other treatment options include selective serotonin-reuptake inhibitors (SSRI) and serotonin and norepinephrine reuptake inhibitors (SNRI), gabapentin, oxybutynin, and other complementary or alternative medicine approaches.[6] However, these treatment modalities are less efficacious as compared to hormone therapy.[6] Currently, paroxetine is the only nonhormonal treatment option to be FDA-approved for the indication of hot flashes. Other complementary or alternative medicine approaches include mind-body interventions (such as hypnosis, cognitive behavioral therapy, relaxation, meditation and aromatherapy), natural products (e.g., herbs, vitamins, minerals and dietary supplements), and whole-system approaches (including traditional Chinese medicine, reflexology, acupuncture, homeopathy).[16] Complementary approaches are not regulated by the FDA and data thus far is mixed for use of herbal supplements and lifestyle modifications for the treatment of VMS.[1] The Menopause Strategies: Finding Lasting Answers for Symptoms and Health clinical trials network evaluated the effect of various complementary methods, including yoga, aerobic exercise, omega-3 fatty acids, and cognitive behavioral therapy, on menopausal symptoms. These trials found that cognitive behavioral therapy was effective in reducing insomnia symptoms for menopausal women with hot flashes, while there was no benefit on VMSs with yoga, exercise, or omega-3 supplementation.[17,18] However, the CBT-Meno randomized controlled trial found that cognitive behavioral therapy for menopausal symptoms showed significantly greater improvements in VMS interference, "bothersomeness," sexual concerns, sleep difficulties, and depressive symptoms.[19]

Menown and Tello and colleagues performed a systematic qualitative review directly comparing NK3R antagonists with SNRIs for the treatment of VMSs. They found that NK3R antagonist administration resulted in a larger reduction from baseline in hot flash frequency, severity, and night sweats as

compared to SNRIs. In addition, they found that NK3R antagonist trials showed good tolerability of the oral medication, while SNRI trials reported increased nausea and overall poor tolerability.[20]

Additionally, hormone therapy is contraindicated in patients who have a history of certain cancers, most notably breast cancer. Women may be experiencing VMS due to oophorectomy or chemotoxic effects on the ovaries. Hormone therapy is also contraindicated in women who have had venous thromboembolism or who have active liver disease or other hepatic impairment. Finally, many women simply do not wish to take hormones for a variety of reasons, even though they are not contraindicated. Thus, the discovery of an effective nonhormonal treatment option, such as an NKB3 receptor antagonist, for VMS provides an encouraging and potentially practice-changing treatment option for all women.

Clinical data to date on NK3R antagonists

Current compounds that target the NK3R include fezolinetant, MLE4901, MT-8554, and Q-122. Fezolinetant is the most studied compound to date. Studies performed by Santoro *et al.*, Fraser *et al.*, and Depypere *et al.*, have shown promising results for fezolinetant and improvement of VMSs.[21–23] Given these compounds are not yet to market, the clinical data are limited and are summarized below. However, studies to date have shown that fezolinetant is generally well-tolerated and safe. Fraser *et al.*[22] reported the most common side effects experienced with fezolinetant to include nausea, diarrhea, fatigue, urinary tract infections, upper respiratory tract infections, sinusitis, headaches, and cough.[22] They reported treatment-related adverse events to include cholelithiasis and drug-induced liver injury. Transient elevations of liver enzymes were followed and rapidly returned to baseline after discontinuation of therapy or trend toward normalization in patients that remained on the study drug.

Targeting of the neurokinin receptors as clinical treatments for VMSs appears to be a highly specific intervention and has led to some promising initial findings. Some basic clinical findings are summarized in the Table 1. No agent is yet

Table 1. Summary Table of VMS Frequency Reduction Achieved With Novel Nonhormonal Agents.

Agent	Target	*N*	Country(ies)/ Continent(s)[a]	Age range	Race/ Ethnicity	Max %VMS reduction	Citation	Length of study	Type of study
MLE4901	NK3R	37	UK	40–62	N/A	72	Prague *et al.*[24]	4 weeks crossover	RCT
Fezolinetant	NK3R	352	USA	40–65	18–33% Black 21–40% Hispanic	87	Fraser *et al.*[22]	12 weeks	RCT
NT-814	NK1/NK3	76	USA	40–65	21% Black	84	Trower *et al.*[25]	2 weeks	RCT
NT-814	NK1/NK3	152	North America, UK	40–65	21% Black	60	Simon *et al.*[26]	12 weeks	
MT-8554 (Elismetrep)	TRPM8	375	North America, Europe, Asia	⩾18	20–31% Black	44	Kingsberg *et al.*[13]	12 weeks	RCT
Q-122	CXCR4, KNDy neurons	21	N/A	30–70	90% Black	59	Painter *et al.*[27]	28 days	Dose escalation
G-CSF	Unknown, multiple anti-inflammatory actions	29	USA	50–65	44% Black	35	Guiahi *et al.*[28]	12 weeks	RCT

[a]Race/ethnicity of study samples are not available for abstract derived data. When available the % of participants who self-identified as Black/African-American or Hispanic/Latino are indicated.
CXCR, chemokine receptor, G-CSF, Granulocyte colony-stimulating factor, KNDy, kisspeptin, neurokinin (NKB), and dynorphin, NK3R, neurokinin-3 receptor, RCT, randomized clinical trial, TRPM8, transient receptor potential melastatin 8 channel, VMS, vasomotor symptom.

available on the market, and thus there is little widespread clinical experience at this point. However, in standardized clinical trials that conform to the FDA guidance for studies of VMS treatment (which includes criteria that participants should have a minimum average of 7 hot flashes a day or 49 per week and the test agent must be compared to a concurrent placebo group), the NK3R antagonist compounds compare favorably to estrogen. This is remarkable, given that none of the nonhormonal alternatives currently available for treating VMS have such efficacy. This class of compounds is, therefore, of great potential interest to menopausal women and the clinicians who care for them.

Initial studies of MLE4901 indicated immediate, highly significant and sustained relief from VMS.[24] A total of 37 women were randomized to MLE4901 or to placebo. Active drug reduced hot flash frequency by 72% by day 3, compared to 20% in the placebo group, and this effect persisted throughout the 4 weeks of initial dosing. After crossover, similar findings were observed. Notably, a significant reduction in VMS frequency was observed (38%) by the third day of dosing, indicating a very rapid onset of effect. Daytime and night-time VMS were analyzed separately, with similar relief during both time periods. An examination of menopausal symptoms using the Menopause-specific Quality of Life Questionnaire and the Hot Flash Related Daily Interference Scale (HFRDIS) indicated rapid and significant improvement.[29,30] Further examination of the domains of these two questionnaires implied that sleep quality was improved by MLE4901 along with the rapid and dramatic reduction in VMS. Further development of MLE4901 was halted due to liver enzyme elevations in some participants.

Fezolinetant has been the most extensively investigated and reported NK3R antagonist to date. In a 12-week, multicenter randomized clinical trial of 87 Belgian women, participants were randomized to 90 mg fezolinetant bid or to placebo. In addition to noting near-immediate improvement in VMS score (a combination of frequency and severity), 12-week results indicated that women randomized to fezolinetant experienced 5.7 hot flashes per week compared to 39 per week in the placebo group.[31] Additional improvements were observed in sleep quality, hot flash daily interference, and overall climacteric symptoms. Adverse events were rare and evenly distributed between active drug and placebo groups.

A subsequent dose-ranging study of fezolinetant included 7 dosing regimens with daily doses of 30–100 mg. Of 352 women who took at least one dose of study medication or placebo, a reduction of VMS of at least 50% was experienced by 81.4–94.7% of women randomized to fezolinetant compared to 58.5% of women randomized to placebo.[22] Per cent reduction in moderate-to-severe hot flash frequency ranged from 74–87% with fezolinetant *versus* 55% with placebo by week 12. Adverse effects were noted again to be rare and evenly distributed across all doses and placebo groups. Endometrial thickness was also monitored in this study, with no evidence of changes related to fezolinetant administration. In a follow-up study (the VESTA trial) addressing patient-reported outcomes, dose-related improvements in the HFRDIS and the Greene Climacteric Scale (GCS) demonstrated treatment-associated responses for active drug greater than placebo throughout the 12-week study.[21,32]

Subsequent studies include the Skylight and Moonlight trials (NCT04003155, NCT04003142, NCT04003389 and NCT04234204), which are currently undergoing preparation for publication. Initial findings in the form of abstracts indicate similar efficacy and safety of fezolinetant in US, Canadian, and European women but not in Chinese women.[33,34] The Moonlight trial, which tested 30 mg daily of fezolinetant compared to placebo in 302 women from China, Japan, and Korea, did not meet its primary efficacy end points at 12 weeks. Based on the overall lower frequency and duration of VMSs and less overall severity seen in Chinese-American women in the Study of Women's Health Across the Nation (SWAN),[35] it is possible that the women recruited for the Moonlight trial had overall less severe symptoms, making it more difficult to measure differences between the placebo and active treatment groups.

Other compounds under investigation for VMS treatment include NT-814, a dual NK1 and three antagonists. In a 2-week US-based Phase 2b randomized trial of 76 postmenopausal women with moderate-to-severe VMS, the two maximal doses of NT-814, 150 mg and 300 mg, caused an 84% and 66% reduction in hot flashes, respectively. Hot flash reduction in the placebo group was 37%.[25]

Other compounds that are in clinical trials include MT-8554 (NCT03291067), which has just completed a 12 weeks, Phase 2 randomized clinical trial with 375 participants.[13] Three doses of elismetrep (1, 5, and 10 mg) were administered to 58, 59 and 58 women, respectively. A total of 54 women were randomized to placebo. By week 12, the 5 mg elismetrep dose resulted in a 42% reduction in VMS frequency compared to a 15% reduction in the placebo group. Safety and tolerability appeared acceptable for women receiving the 5 mg dose.

Q-122 is another related compound under investigation for its usefulness in treating VMS in women with breast cancer. It does not target the NK3R, but it does inhibit the firing of the kisspeptin–neurokinin–dynorphin (KNDy) neurons in the brain. It is a CXCR4 modulator. In Phase 1b study of Q-122, 21 women with breast cancer who were taking tamoxifen or an aromatase inhibitor were administered Q-122 for 28 days with potential dose escalation (from 100 to 200 mg a day) for a second 28 days period.[27] A 59% reduction in VMS frequency was observed, along with improvements in the GCS. No adverse side effects were reported. A Phase 2 clinical trial is currently underway (NCT03518138).

Granulocyte colony-stimulating factor (G-CSF) has also been investigated as a possible nonhormonal treatment for VMS.[28] In a 12 week pilot trial of a single dose, G-CSF was given to 19 women and 10 received placebo. A statistically significant 35% reduction in hot flashes was observed at 2 weeks in the treated group *versus* 5% in the placebo group. G-CSF does not have a verified mechanism of action but has overall anti-inflammatory effects. Further trials are currently underway (NCT03640754).

Taken together, the newer NK targeting compounds appear to have high efficacy against VMS and reduce both frequency and severity. When additional measures have been sought, there appears to be an improvement in sleep, particularly for the NK3R antagonists. Whether these promising early findings will carry over into the clinic remains to be seen, but enthusiasm is overall high for agents that have comparable efficacy to hormone therapy but can be used in women who cannot or will not take hormones.

Summary and conclusions

VMS is a hallmark symptom of menopause and constitutes a substantial burden to many women due to their ability to disrupt daily activities, negatively impact sleep and mood, and overall decrease quality of life. Despite decades of research, the anatomical source of VMS has only recently been localized to the KNDy neurons in the hypothalamus. Prior to this discovery, estrogen was the mainstay for the treatment of VMS and, for many years, was the only FDA-approved treatment for VMS. Women in whom estrogen was contraindicated were, therefore, often without recourse.

The subsequent discovery of nonhormonal agents that were effective for the treatment of VMS relied upon serendipity—women would present to their clinician noting that their VMS improved with the introduction of a new medication for an entirely different purpose. In this manner, nonhormone treatments such as the SSRI/SNRI class of drugs, used for depression, gabapentin, used for neuropathic pain and sleep, and oxybutynin, used for irritable bladder, were eventually systematically tested in randomized clinical trials. These latter agents are backed by substantial medical evidence for efficacy. Despite these additional clinical trials, however, only one other agent, paroxetine mesylate, went through the arduous process of FDA approval for the treatment of VMS.

Targeting the NK3R on the KNDy neuron has proven to be a successful strategy for reducing or eliminating the bothersome VMS associated with menopause. Early trials have been hampered by adverse events for some agents, but others in development appear well on their way to FDA approval. Agents that target other neurokinin receptors, combinations of neurokinin receptors, the entire KNDy neuron, or other immune and inflammatory pathways are also under investigation. Hopefully, a new era in the treatment of VMS will be opened up by these exciting scientific advances.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Author contributions
Melissa Conklin: Conceptualization; Data curation; Investigation; Project administration; Writing – original draft; Writing – review & editing.

Nanette Santoro: Conceptualization; Data curation; Investigation; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

Acknowledgements
Not applicable.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
Melissa Conklin declares that there is no conflict of interest. Dr. Nanette Santoro has the following disclosures: Consultant: Ansh Labs; Scientific Advisory Board: Astellas, Que Oncology, Amazon (Ember), Menogenix, Inc.; Grant support: Menogenix, Inc.

Availability of data and materials
Not applicable.

References
1. ACOG Practice Bulletin No. 141: management of menopausal symptoms. *Obstet Gynecol* 2014; 123: 202–216.
2. Williams RE, Levine KB, Kalilani L, *et al.* Menopause-specific questionnaire assessment in US population-based study shows negative impact on health-related quality of life. *Maturitas* 2009; 62: 153–159.
3. Dibonaventura MD, Wagner JS, Alvir J, *et al.* Depression, quality of life, work productivity, resource use, and costs among women experiencing menopause and hot flashes: a cross-sectional study. *Prim Care Companion CNS Disord* 2012; 14: PCC. 12m01410.
4. Avis NE, Crawford SL, Greendale G, *et al.* Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med* 2015; 175: 531–539.
5. Santoro N, Epperson CN and Mathews SB. Menopausal symptoms and their management. *Endocrinol Metab Clin North Am* 2015; 44: 497–515.
6. Morrow PK, Mattair DN and Hortobagyi GN. Hot flashes: a review of pathophysiology and treatment modalities. *Oncologist* 2011; 16: 1658–1664.
7. Mittelman-Smith MA, Williams H, Krajewski-Hall SJ, *et al.* Role for kisspeptin/neurokinin B/dynorphin (KNDy) neurons in cutaneous vasodilatation and the estrogen modulation of body temperature. *Proc Natl Acad Sci USA* 2012; 109: 19846–19851.
8. Rance NE, Dacks PA, Mittelman-Smith MA, *et al.* Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: a novel hypothesis on the mechanism of hot flushes. *Front Neuroendocrinol* 2013; 34: 211–227.
9. Gaubert M, Marlinge M, Kerbaul F, *et al.* Adenosine plasma level and A2A receptor expression in patients with cardiogenic shock. *Crit Care Med* 2018; 46: e874–e880.
10. Modi M and Dhillo WS. Neurokinin 3 receptor antagonism: a novel treatment for menopausal hot flushes. *Neuroendocrinology* 2019; 109: 242–248.
11. Prague JK, Roberts RE, Comninos AN, *et al.* Neurokinin 3 receptor antagonism as a novel treatment for menopausal hot flushes: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; 389: 1809–1820.
12. Crandall CJ, Manson JE, Hohensee C, *et al.* Association of genetic variation in the tachykinin receptor 3 locus with hot flashes and night sweats in the women's health initiative study. *Menopause* 2017; 24: 252–261.
13. Kingsberg SM, Goldstein S, Simoncini T, *et al.* A clinical study to evaluate Elismetrep (TRPM8 antagonist), a non-hormonal drug for the treatment of vasomotor symptoms in postmenopausal women. *North American Menopause Society 2020 Annual Meeting*, Abstract S-13. Published in Menopause 2020; 17: 1447–1475.
14. Rossouw JE, Anderson GL, Prentice RL, *et al.* 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.
15. Salpeter SR, Walsh JM, Greyber E, *et al.* Brief report: coronary heart disease events associated with hormone therapy in younger and older

women. A meta-analysis. *J Gen Intern Med* 2006; 21: 363–366.

16. Johnson A, Roberts L and Elkins G. Complementary and alternative medicine for menopause. *J Evid Based Integr Med* 2019; 24: 2515690X19829380.
17. Guthrie KA, Larson JC, Ensrud KE, *et al.* Effects of pharmacologic and nonpharmacologic interventions on insomnia symptoms and self-reported sleep quality in women with hot flashes: a pooled analysis of individual participant data from four MsFLASH trials. *Sleep* 2018; 41: zsx190.
18. Reed SD, LaCroix AZ, Anderson GL, *et al.* Lights on MsFLASH: a review of contributions. *Menopause* 2020; 27: 473–484.
19. Green SM, Donegan E, Frey BN, *et al.* Cognitive behavior therapy for menopausal symptoms (CBT-Meno): a randomized controlled trial. *Menopause* 2019; 26: 972–980.
20. Menown SJ and Tello JA. Neurokinin 3 receptor antagonists compared with serotonin norepinephrine reuptake inhibitors for non-hormonal treatment of menopausal hot flushes: a systematic qualitative review. *Adv Ther* 2021; 38: 5025–5045.
21. Santoro N, Waldbaum A, Lederman S, *et al.* Effect of the neurokinin 3 receptor antagonist fezolinetant on patient-reported outcomes in postmenopausal women with vasomotor symptoms: results of a randomized, placebo-controlled, double-blind, dose-ranging study (VESTA). *Menopause* 2020; 27: 1350–1356.
22. Fraser GL, Lederman S, Waldbaum A, *et al.* A phase 2b, randomized, placebo-controlled, double-blind, dose-ranging study of the neurokinin 3 receptor antagonist fezolinetant for vasomotor symptoms associated with menopause. *Menopause* 2020; 27: 382–392.
23. Depypere H, Lademacher C, Siddiqui E, *et al.* Fezolinetant in the treatment of vasomotor symptoms associated with menopause. *Expert Opin Investig Drugs* 2021; 30: 681–694.
24. Prague JK, Roberts RE, Comninos AN, *et al.* Neurokinin 3 receptor antagonism rapidly improves vasomotor symptoms with sustained duration of action. *Menopause* 2018; 25: 862–869.
25. Trower M, Anderson RA, Ballantyne E, *et al.* Effects of NT-814, a dual neurokinin 1 and 3 receptor antagonist, on vasomotor symptoms in postmenopausal women: a placebo-controlled, randomized trial. *Menopause* 2020; 27: 498–505.
26. 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.
27. Painter W, Speed AL, Phillips K, *et al.* Results of a phase Ib study of Q-122 treatment of vasomotor symptom in breast cancer patients. *J Clin Oncol* 2015; 33(suppl. 28): 99.
28. Guiahi MW, Schechter CA, Duke DM, *et al.* Can human recombinant granulocyte colony-stimulating factor improve menopausal hot flashes? Results from a pilot study. In: *Society for reproductive investigation 62nd annual meeting*, San Francisco, CA, March 25–28 2015, LB–022.
29. Hilditch JR, Lewis J, Peter A, *et al.* A menopause-specific quality of life questionnaire: development and psychometric properties. *Maturitas* 1996; 24: 161–175.
30. 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 Manag* 2001; 22: 979–989.
31. Depypere H, Timmerman D, Donders G, *et al.* Treatment of menopausal vasomotor symptoms with fezolinetant, a neurokinin 3 receptor antagonist: a phase 2a trial. *J Clin Endocrinol Metab* 2019; 104: 5893–5905.
32. Greene JG. A factor analytic study of climacteric symptoms. *J Psychosom Res* 1976; 20: 425–430.
33. https://www.astellas.com/en/news/25421
34. https://www.astellas.com/en/system/files/news/2022-03/20220315_en_1_2.pdf
35. Tepper PG, Brooks MM, Randolph Jf Jr, *et al.* Characterizing the trajectories of vasomotor symptoms across the menopausal transition. *Menopause* 2016; 23: 1067–1074.