Neurokinin-Targeted Therapy: A New Era for the Management of Vasomotor Symptoms Associated with Menopause? Interviews with Three Key Opinion Leaders

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PHARMA PARTNERSHIP

Interview Summary

Millions of women enter menopause each year, representing one point in a continuum of life stages that marks the end of their reproductive years. Vasomotor symptoms (VMS) during menopause, primarily hot flashes, or night sweats if occurring at night, represent a key area of clinical concern, with a third of women reporting moderate-to-severe symptoms. Alongside VMS, many women also struggle with disrupted sleep during menopause, the combination of which can significantly impact quality of life (QoL) outcomes. VMS and sleep disturbance during menopause have been linked to impaired cognitive function, fatigue, anxiety, and depression. That being said, a large proportion of women do not currently receive treatment, driven by a range of factors, including clinical contraindication or personal preference. Neurokinin-targeted therapies (NKT) have emerged as a novel class of therapy, targeting receptors within the hypothalamus which play a role in thermoregulation and the pathophysiology of VMS during menopause. This new class of treatment provides a much-needed alternative therapy for underserved populations, including patients undergoing adjuvant endocrine therapy (AET) due to hormone receptor (HR)-positive breast cancer, for which the standard of care hormone therapy is contraindicated.

For this article, EMJ conducted interviews in March and April 2026 with three key opinion leaders: Rossella Nappi, University of Pavia, IRCCS San Matteo Foundation Hospital, Italy; Victor Navarro, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts, USA; and Donal Brennan, University College Dublin School of Medicine and Mater Misericordiae University Hospital, Ireland, all of whom have a wealth of experience and expertise in women's health. The experts share their valuable insights on the impact of VMS and sleep disturbances on women's QoL, alongside the unmet needs associated with traditional treatment strategies. The experts also delve into the underlying pathophysiology of VMS and sleep disturbances, outlining the current scientific understanding at the level of the hypothalamus, and providing evidence for NKTs, differentiating among neurokinin-1 (NK1) and neurokinin-3 (NK3) receptors, and between NK3 receptor antagonists and dual-NK1 and NK3 receptor antagonists. Further discussion addresses the unmet needs and management of VMS associated with endocrine therapy (ET) in HR-positive breast cancer.

INTRODUCTION

Menopause is caused by a loss of ovarian follicular function and a decline in circulating blood oestrogen levels, and is associated with a range of possible symptoms affecting multiple biological systems.[1,2] Up to 80% of women experience VMS, primarily hot flashes, or night sweats if occurring at night, due to altered hypothalamic thermoregulation, with a third reporting moderate-to-severe symptoms.[3,4] The median duration of these symptoms is over 7 years, but they may persist for up to 15 years.[5] VMS has been linked to a number of QoL outcomes, including mood disturbance, impaired cognitive function, fatigue, anxiety, and depression.[6,7] Up to 60% of women also struggle with disrupted sleep during menopause, including poor sleep quality, insufficient sleep duration, obstructive sleep apnoea, restless legs syndrome, and insomnia.[8,9] Sleep disturbance during menopause is associated with increased healthcare costs and negative outcomes, including a significantly decreased QoL, poor work performance, and symptoms of low mood and anxiety.[10,11] Since not all women who experience moderate-to-severe VMS seek healthcare advice,[3] the reported burden is likely to be significantly underestimated, and represents a considerable and under-recognised unmet clinical need, one which has recently attracted considerable research interest.[12,13]

CURRENT TREATMENT LANDSCAPE

Hormonal Therapy

The mainstay of traditional therapy for menopause VMS is menopause hormone therapy (MHT), which replenishes declining levels of endogenous hormones (oestrogen, progesterone, and, in some instances, androgens) to reduce symptom burden.[14] According to the North American Menopause Society (NAMS) Hormone Therapy Position statement,[15] hormone therapy remains the most effective treatment for VMS and the genitourinary syndrome of menopause, and has been shown to prevent bone loss and fracture.[15]

While MHT represents the 'gold' standard for alleviating symptoms of VMS, its use is influenced by several safety considerations. For the following groups, for example, MHT is contraindicated: women who have unexplained bleeding from the genital tract, acute liver failure or active liver disease, deep vein thrombosis, uterine cancer, ovarian cancer, history of coronary heart disease, stroke, myocardial infarction, or HR-positive breast cancer.[3,16] For further subgroups indicating increased clinical risk, including women with other subtypes of breast cancer, high cholesterol or triglycerides, migraines, or diabetes, further analysis to inform risk–benefit assessment is required.[14,17] Treatment should be individualised to identify the most appropriate type, dose, formulation, route of administration, and duration of use, utilising the best available evidence to enable maximum benefits and minimum risks.[15] MHT is generally not recommended for use after the age of 60 years or after 10 years into menopause, and many women choose not to take MHT, therefore, there is an unmet need for safe and effective non-hormonal options to treat VMS.[18]

Non-hormonal Treatments

Alternative, non-hormonal treatment options include selective serotonin-reuptake inhibitors (SSRI) and serotonin and norepinephrine reuptake inhibitors, gabapentin, and oxybutynin, along with complementary or alternative medicine approaches such as cognitive behavioural therapy or hypnosis.[19,20] However, such treatment modalities are often used off-label, are less efficacious, and tolerability issues have been reported.[21,22] While VMS can significantly impact QoL,[6] a significant proportion of women do not receive treatment.[3] Real-world evaluation of treatment utilisation by women experiencing VMS associated with menopause in the USA and Europe reported that nearly a third of women with moderate-to-severe VMS had never received treatment despite access to healthcare, with women commonly turning to over-the-counter products or lifestyle changes to try and alleviate their symptom burden.[23] Nappi explains that many women don't want to or cannot take

hormone therapy, either because it is clinically contraindicated or due to personal preference, leaving a significant population underserved. Navarro also highlights further groups who may benefit from alternative treatments for VMS, including men on androgen deprivation therapy and adolescents on puberty blockers. Gaps in this treatment landscape represent an unmet clinical need for new and effective non-hormonal treatment options, with clear data on efficacy in managing VMS and concomitant sleep and mood symptoms to improve QoL.

IMPACT ON QoL

The impact of VMS on QoL has been widely reported across diverse populations.[3,6,24,25] Nappi explains that the symptoms of menopause can be highly disruptive, impacting women's daily functional and cognitive abilities due to associated sleep disruption, low mood, and brain fog, and affecting both how they feel and how they behave. Less reported symptoms can include vaginal dryness, low libido, and genitourinary symptoms, which Nappi explains as having a significant impact on a woman's personal relationships and self-esteem.[26] Brennan highlights this as extremely detrimental to overall QoL outcomes. Many of the symptoms of menopause are considered multifactorial, explains Brennan, with overlapping mechanisms of explanation that cannot all be attributed to the menopause alone. For example, menopausal women experiencing sleep disturbances may also experience problems with mood and cognition, which may or may not be caused directly by menopause, or indirectly by the associated sleep disturbance. Research indicates that the severity of VMS is associated with an increase in sleep disturbance, worse sleep quality, and greater impairment to daytime activities and work productivity.[27] Qualitative research capturing the lived experiences of women experiencing VMS describes the burden symptoms pose on daily life, including their negative impact on mental health, ability to work, social life, physical comfort, and emotional wellbeing, and an increase in feelings of frustration, embarrassment, and anxiety.[28]

Symptom Variability

Menopause can be split into three main categories: natural menopause, occurring spontaneously with age; surgical menopause, following oophorectomy;[29] and menopause symptoms caused by medical treatments, such as AET or chemotherapy.[30,31] While the symptoms of natural, surgical, and treatment-related menopause are largely the same, the severity and impact of symptoms can differ greatly. Nappi explains that each individual case must be assessed accordingly, conscious of the woman's life stage; any potential trauma associated with onset, diagnosis, or treatment; and the abruptness of hormonal change, particularly in cases of surgical menopause symptoms or caused by AET, where VMS symptoms can be more severe and treatment options may be limited.[32] Hormonal changes during menopause affect multiple biological systems, with symptoms including central nervous system-related disorders; metabolic, weight, cardiovascular, and musculoskeletal changes; urogenital and skin atrophy; and sexual dysfunction.[33]

HEALTH-SEEKING BEHAVIOURS AND BARRIERS TO CARE

Symptoms of menopause often begin during perimenopause, which encompasses the menopausal transition and the first year after the final menstrual period, a period of time marked by profound reproductive and hormonal changes.[34] While menopause is often marked by 12 consecutive months of amenorrhoea,[35] Nappi explains that many women miss periods for different reasons, which makes it difficult in some instances to earmark the menopausal transition accurately, leading many women not to seek healthcare professional advice. Despite the prevalence and burden of symptoms, only around 54% of women seek medical input.[36,37] More than half of women do not approach their primary healthcare provider for help or advice during menopause,[38] a condition that has been 'shrouded in silence' for many years.[39] Nappi explains that this is extremely common in her experience, highlighting that she feels women wait far too long before seeking additional support. Barriers to seeking help for symptoms of

menopause include a lack of knowledge of the full range of symptoms and available treatments, stigma, embarrassment, and the belief that it is part of normal ageing.[38] Qualitative research with perimenopausal and menopausal women also reported that women often do not feel empowered to seek healthcare advice due to concerns over feeling dismissed or not being offered options for treatment, including both hormonal and non-hormonal options.[38]

Nappi explains that menopause is a natural stage in women's lives, and while many women would love to get rid of their symptoms, a lot of women don't want to take hormones to manipulate their reproductive health. She explains the importance of women starting an open dialogue with their healthcare provider during perimenopause, allowing sufficient time to fully discuss the experience of menopause, including the benefits and risks of the different treatment options used in real-world practice, based on the patient's individual symptom severity and clinical circumstances. She goes on to explain that treating menopause is not just about treating symptoms; it involves assessing a range of risk factors that can be addressed through early intervention, including an increase in cholesterol and glucose levels, and the potential development of insulin resistance or hypertension.[40] Nappi explains that delaying intervention makes these changes more difficult to reverse because body systems may have already adapted to the menopausal changes. She advocates for a proactive, individualised approach to menopause care, where women are engaged, informed, and supported to implement preventative strategies, and appropriate VMS treatment decisions are based on individual needs and preferences.

THE SCIENCE BEHIND MENOPAUSE

Our understanding of the science behind menopause has changed exponentially over the last decade. Previously, little was known about the science behind VMS beyond the decline in oestradiol, the body's most potent natural oestrogen.[41] We now understand that fundamental changes occur at the level of the hypothalamus during menopause, contributing to the development of VMS. Navarro highlights that early preliminary research into kisspeptin, neurokinin B, and dynorphin (KNDy) neurones laid the foundation for our current understanding.[42] Named after the three neuropeptides they produce, KNDy neurones are largely responsible for gonadotropin-releasing hormone (GnRH) pulse generation, a process established during puberty to regulate the release of reproductive hormones, which is tightly controlled by oestradiol feedback.[43,44] Navarro explains that while he was presenting a seminar at the University of Washington, Seattle, USA, in 2009 or 2010 on GnRH pulse generation and KNDy neurone involvement during puberty, a clinician in the audience raised the observation that hot flashes during menopause often correlate with luteinising hormone pulses driven by GnRH pulse generator activity, sparking the question of how these processes might be linked. This initial conversation has since led to over a decade of research uncovering the role of KNDy neurones in the generation of VMS. During the menopausal transition, these KNDy neurones, which project to and regulate GnRH neurones, are triggered to compensate for falling oestradiol levels, and therefore become hyperactive and hypertrophic. This is accompanied by upregulation of NK1 and NK3 receptors and their respective ligands, substance P and neurokinin B. Neurokinin B, which acts on NK3 receptors in the thermoregulatory neurones, triggers heat-dissipation responses, including vasodilation of the skin, resulting in hot flashes.[45-47] Navarro explains that while there are still many aspects of this process we do not fully understand, the characterisation of KNDy neurones in this process has been a remarkable example of translational research, filling a significant gap in our understanding and resulting in the development of NKTs. Nappi remarks that this population of KNDy neurones, which is activated during puberty, acts as the gatekeeper of reproductive life, including the onset of menarche (the first instance of menstruation), and also marks the transition into fertility, and it is fascinating that the

same system becomes active again during menopause, as reproductive life comes to an end. Navarro explains that while the pathways behind VMS are becoming clear, the science underlying menopause-related sleep disturbance is less well understood. It is thought that the same process whereby hyperactivity of KNDy neurones increases production of neurokinin B, the respective ligand of thermoregulatory NK3 receptors, may also upregulate substance P, the ligand for NK1 receptors, which is highly distributed throughout the brain in regions involved in sleep regulation.[48] Peripheral NK1 receptors are also found on nerves associated with blood vessels in the skin, and contribute to sweating and vasodilation as a cooling response to the increase in body temperature.[47]

NEUROKININ-TARGETED THERAPIES

NKTs are a class of neurokinin receptor antagonists, which are designed to specifically target the receptors expressed by KNDy neurones. Neurokinin receptors are expressed in the hypothalamus, but can also be found in peripheral tissues, including NK1 receptor expression in the skin.[49]

Dual NK1 and NK3 Receptor Antagonist

The latest science indicates that by targeting both NK1 and NK3 receptors centrally in the hypothalamus, and NK1 receptors peripherally in the skin, elinzanetant, a dual NK1 and NK3 receptor antagonist, helps restore balance to both temperature regulation, and, additionally, sleep. Following results from the robust Phase III OASIS clinical research programme, including OASIS 1 and 2 (NCT05042362/NCT05099159)[49] and OASIS 3 (NCT05030584),[50] elinzanetant has so far been approved in the USA, EU, UK, Canada, Australia, and Switzerland for the treatment of moderate-to-severe VMS associated with menopause. The OASIS 1–3 programme includes combined data from approximately 1,400 women with moderate-to-severe VMS resulting from natural or surgical menopause. Results of OASIS 1 demonstrated a statistically significant and clinically meaningful reduction in VMS frequency as early as Week 1 (key secondary endpoint) and at Weeks 4 and 12 (co-primary endpoint), with an approximately 65% reduction in VMS frequency at Week 12 versus approximately 42% for placebo. Significant reductions were also seen for VMS severity at Weeks 4 and 12 (co-primary endpoint), and improvements were maintained during the 26-week treatment period. Similar results were achieved in OASIS-2. Elinzanetant also significantly improved sleep disturbances and menopause-related QoL at Week 12 (key secondary endpoints), and descriptive analyses during OASIS 3 showed numerical advantages for elinzanetant versus placebo for improving both VMS frequency and severity over 50 weeks, and sleep disturbances and menopause-related QoL over 52 weeks (exploratory endpoints), with a significant reduction in VMS frequency demonstrated at Week 12 (primary endpoint).

Nappi explains that, for the first time in her 35-year career as a gynaecologist, a new class of treatment has been developed. She explains that the development of an alternative treatment option, one which has been studied specifically to relieve VMS associated with menopause, represents a step forward for women, particularly those for whom hormone therapy is contraindicated. Navarro explains that while this evidence is compelling, the improvement of sleep from NK1 receptor antagonism may be either a direct or indirect effect, as improvements in sleep could be secondary to a reduction in VMS, which are considered highly disruptive to sleep.

Selective NK3 Receptor Antagonist

Fezolinetant, a selective NK3 receptor antagonist, works by inhibiting neurokinin B from binding to its receptor in the hypothalamus. In clinical trials, fezolinetant has also been shown to reduce the frequency of VMS.[51] Fezolinetant was approved in 2023 in the USA, EU, UK, and Switzerland for the treatment of moderate-to-severe VMS due to menopause, following evidence from the

Phase III SKYLIGHT 1 (NCT04003155)[52] and SKYLIGHT 2 (NCT04003142)[53] trials, and, additionally, the SKYLIGHT 4 safety trial (NCT04003389).[54] SKYLIGHT 1 and 2 included approximately 1,000 women with moderate-to-severe VMS resulting from natural or surgical menopause with the same co-primary endpoints as were used in the OASIS clinical trials with elinzanetant. In the SKYLIGHT 1 and 2 trials, fezolinetant significantly reduced both the frequency and severity of VMS compared to placebo as early as Week 1, and at Weeks 4 and 12, and improvements were sustained over the 52-week treatment period.[53] Some improvements were also seen for menopause-related QoL (exploratory endpoint) and sleep (key secondary endpoint); however, the magnitude and statistical significance of the effect on sleep varied by study and fezolinetant dose.

Navarro explains that the results of this research provide the clearest evidence for the role of neurokinin signalling in VMS development, consolidating our understanding of this mechanism and informing the development of next-generation non-hormonal therapies. This new class of drug has expanded therapeutic options for women during menopause, addressing diverse clinical needs and patient preferences, and marks a milestone discovery in the management of VMS during menopause.

Safety Considerations

According to Navarro, the clinical trials for both elinzanetant and fezolinetant have been well controlled, affirming that these compounds have a favourable safety profile.

The OASIS 3 trial of elinzanetant reported no association with hepatotoxic effects, no incidences of endometrial hyperplasia, endometrial neoplasms, or meaningful changes in bone density or bone turnover markers (NCT05030584).[50] The majority of treatment-emergent adverse events (TEAE) were considered mild or moderate, and the most frequently reported that were considered to be treatment related were somnolence, fatigue, and headache.

Most adverse events identified during the SKYLIGHT 4 safety trial of fezolinetant (NCT04003389)[54] were mild or moderate in severity. The most common TEAEs occurring more frequently with fezolinetant 45 mg than with placebo were abdominal pain, diarrhoea, and insomnia.[55] Occurrence of endometrial hyperplasia or malignancy was equal to or lower than 1%, changes in bone mineral density were similar across treatment groups, and there was no evidence of liver function impairment or liver-associated symptoms, including Hy's law cases.

Liver Safety

Liver safety is a TEAE of special interest in NKT development, which Navarro explains as being linked to liver toxicity induced by first-generation NK3 antagonists, which have since been discontinued.

Due to elevations in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) that had been observed in clinical trials with fezolinetant, and serious cases with elevations of ALT and/or AST (>10x upper limit of normal) with concurrent elevations in bilirubin and/or alkaline phosphatase having been reported post-marketing, monthly liver function tests must be performed during the first 3 months of treatment, and thereafter based on clinical judgement.[56]

Recently published data specific to liver safety of elinzanetant[57] indicate a low risk of liver toxicity, with no imbalance seen in the clinical programme (Phases I–III) between the elinzanetant and placebo groups for ALT or AST elevations up to 5×, 10×, or 20× the upper limit of normal. In addition, there were no cases meeting Hy's law, and no indication of cholestatic injury. Based on these findings, the independent liver safety monitoring board concluded that liver monitoring is considered unnecessary in clinical practice. Navarro adds that data indicate that there is no expression of the NK3 receptor in the liver, and only minor expression of the NK1 receptor, indicating that hepatotoxicity should not be viewed as an on-target effect of NK1 and NK3 receptor antagonists.[57]

MANAGING MENOPAUSAL SYMPTOMS IN PATIENTS UNDERGOING AET DUE TO HR-POSITIVE BREAST CANCER

HR-positive early (Stages I, II, or IIIA) breast cancer accounts for over 70% of cases worldwide, and is associated with a persistent risk of relapse up to 20 years post-diagnosis and treatment.[58,59] While treatment is individualised based on tumour stage and biology, AET is considered a foundational treatment approach for HR-positive breast cancer, targeting oestrogen and/or progesterone receptors to inhibit cancer growth.[60] According to European Society for Medical Oncology (ESMO) Clinical Guidelines,[61] AET is almost universal for patients with HR-positive breast cancer, reducing the risk of locoregional recurrence, distant metastatic recurrence, and contralateral breast cancer. AET is typically prescribed for a minimum of 5 years, and can be extended to 10 years for patients with larger or higher-grade initial tumour presentation. AET includes tamoxifen, a selective oestrogen receptor modulator, and aromatase inhibitors such as anastrozole, letrozole, or exemestane.[61,62] Despite the benefits of AET in promoting disease-free survival,[63] oestrogen deprivation as a result of AET often leads to the development of treatment-induced VMS, including hot flashes and night sweats,[62] which can have a significant impact on QoL during treatment. Brennan explains that this represents a significant clinical challenge, as there are a number of historical studies showing that women who have a history of breast cancer cannot be put on MHT due to an increased risk of disease recurrence.[64] While women in breast cancer remission receiving AET experience highly exacerbated VMS and concomitant symptom burden, 40.4% do not receive VMS treatment.[65] This unmet need results in a large proportion of patients not adhering to AET due to uncontrolled VMS: up to 40% of patients discontinue the medication early, and 30% of patients take the medication less frequently than directed, increasing their risk of disease recurrence.[66] Brennan indicates that while it's difficult to really understand this data, because a lot of the studies are based on patient recall, which is not always accurate in the context of non-adherence, it is broadly understood that patients who are not adherent to AET have worse clinical outcomes from a breast cancer perspective.[67]

Clinical Context and Alternative Therapies

Brennan explains that in specific cases, for example, a patient with oestrogen receptor–negative breast cancer who has had a bilateral mastectomy and a long treatment-free interval, it may be possible to consider MHT. However, he urges that this is not routine and should only be explored on an individual basis after all non-hormonal options have been exhausted, with any decision made collaboratively between the patient, their oncologist, and a gynaecologist or menopause specialist. Brennan explains that alternative treatments for VMS in this context have traditionally relied on the use of non-hormonal, often off-label or unlicensed medications, including the use of antidepressants such as SSRIs and serotonin and norepinephrine reuptake inhibitors,[68] oxybutynin therapy,[69] or gabapentin.[70] Brennan indicates that such treatments can cause a number of side effects and are often poorly tolerated by patients. Women with a history of breast cancer taking tamoxifen should avoid paroxetine, an SSRI which has been shown to interfere with tamoxifen metabolism.[68] However, other SSRIs are better tolerated in this context. Non-pharmacological alternatives include cognitive behavioural therapy, hypnosis, or acupuncture, with limited evidence. This clinical challenge represents a clear gap for new non-hormonal alternatives with established safety profiles in this population, which Brennan agrees may be filled by the development of neurokinin receptor antagonists.

Evidence for the Use of NKT in This Context

The use of fezolinetant is currently under investigation regarding its safety and efficacy in patients with HR-positive breast cancer receiving AET (NCT06440967),

and is therefore not yet approved in this patient population.

OASIS 4 represents a robust Phase III trial to determine the effects of elinzanetant in treating VMS in this patient population, with published findings supporting its approval in this population so far in the EU.[71,72] Brennan emphasises that this research, being progressed specifically in patients with breast cancer represents a step forward for the breast cancer community, addressing a long-standing unmet need. Outlining the results, Brennan explains that patients with a history of breast cancer receiving AET were assigned in a 2:1 ratio to elinzanetant or placebo for 12 weeks, before all patients crossed over to active treatment for another 40 weeks and were offered the opportunity to continue treatment with elinzanetant for an additional 2 years. The primary endpoint was the change in frequency of VMS at 4 and 12 weeks, where elinzanetant demonstrated a significantly lower frequency of VMS associated with AET compared with placebo, including a mean reduction of 7.8 symptom episodes at 12 weeks versus 4.2 with placebo.[71] Brennan points out that a large proportion (over 90%) of participants chose to continue into the 2-year extension study, which he suggests is indicative of good tolerability, sustained benefit, and potential improvements in QoL outcomes. Results of this study suggest that elinzanetant is an efficacious treatment for VMS associated with AET, with a favourable safety profile. Brennan explains that data from OASIS 4 identified a stable adherence to AET; however, as one of the inclusion criteria for that study was that the patients had to be on AET, this may be a reflection of trial inclusion criteria rather than an outcome of treatment. While Brennan emphasises that further real-world evidence is needed to determine the influence of NKT on long-term AET adherence, he considers that the impact will be positive, and adherence should be considered an important endpoint alongside traditional treatment outcomes. Brennan also considers the need to conduct further research on the impact of NKT in patients with late-stage or metastatic breast cancer, to open up this treatment option to further cohorts.

Future Directions and Impact

NKTs could represent a new era for the management of VMS associated with menopause. Previously, the conversation was MHT or no MHT, or a range of alternative treatment options with a low evidence base. Navarro explains that the use of MHT is like painting on treatment with a broad brush, while NKT is like using a pencil, precisely addressing the onset of VMS without influencing other physiological processes. He highlights that while both have their place in the management of VMS associated with menopause, NKT represents an option for a large proportion of patients for whom MHT is not suitable. Nappi considers that these novel therapies provide us with a much-needed new narrative. Many women want to get rid of VMS symptoms and live their lives unburdened, and Nappi considers a drug that is specifically designed to stop the development of these symptoms to be a powerful tool in clinical practice. She sees the future of menopause management in combination, with either MHT or NKT prescribed alongside treatments for vaginal, bone, cardiovascular, and metabolic health, facilitating a holistic and preventative approach to women's health and wellbeing.

Nappi would like to see if NKT might help to relieve symptoms associated with perimenopause, considering the importance of real-world data to drive our understanding of these novel therapies. Brennan agrees, considering that real-world data will elucidate our understanding of the side effects of treatment, and urges the importance of implementing these new therapies in an evidence-based manner. Clinicians will need clear guidance and data on adverse events and clinical drug interactions to ensure appropriate use in clinical practice. Ultimately, Brennan highlights the importance of ensuring that the patient's voice is heard. He recognises that it has historically been overlooked when considering the severity of VMS and the impact on QoL outcomes, and considers that this novel therapy presents an opportunity to co-develop educational approaches, placing the patient at the centre of educational initiatives, which comes into focus when introducing new treatments or drug classes into clinical practice.

Navarro explains that while progress has been made over the last decade, there is still so much to learn about menopause, including why some women have more severe VMS symptoms than others, what determines that difference in severity, number, and the onset of hot flashes, and what drives the mechanism that endogenously ends these symptoms altogether. Navarro concludes by highlighting that what may seem like a 5-year breakthrough in clinical drug development is actually over 20 years in the making, based on preliminary research to characterise KNDy neurones, and progressing through multiple preclinical models before entering late phase research and ultimate drug approval. This underscores the importance of early phase research, which may be overlooked at conferences and in medical journals, but is foundational to every new therapeutic discovery and requires greater public and governmental support.

CONCLUSION

Up to 80% of women experience VMS during menopause, primarily hot flashes, or night sweats if occurring at night, but many also experience sleep disturbances. A third of women report moderate-to-severe symptoms affecting daily life. VMS is well-documented to negatively impact QoL outcomes, including mental health, mood, cognition, personal relationships, ability to work, and daily functioning. The first-line standard of care treatment for VMS is hormone therapy; however, in a significant proportion of cases, this treatment is either clinically contraindicated, such as in the case of HR-positive breast cancer, or women choose not to take it for personal reasons. This represents one of the longest-standing challenges in women's healthcare, subject to years of less efficacious or unavailable alternative treatment options. This gap in care has recently been filled through the development of NKTs, which target the underlying pathophysiological mechanism of VMS at the level of the hypothalamus. Clinical research is compelling, and recent approvals of both elinzanetant, a dual NK1 and NK3 receptor antagonist, and fezolinetant, a selective NK3 receptor antagonist, could mark a new era for the management of VMS associated with menopause.

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