Editorial

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Revolutionary treatment for menopausal symptoms: Veozah (Fezolinetant) receives FDA approval

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Introduction

Menopause is described as the absence of spontaneous menstruation for over 12 months. Every year, 1.5 million women undergo the menopausal transition, frequently involving vasomotor symptoms (VMS) such as vaginal dryness, decreased libido, sleeplessness, lethargy, and joint pain[1]. Additionally, significant issues with sleep, living conditions, and depression are connected to moderate-to-severe VMS[2]. Up to 55% of women can have hot flashes even before the monthly irregularity signifies the beginning of the menopausal transition. Their frequency and intensity increase as women go through menopause, peaking during the final transition and dropping off during the following few years[3]. Hot flashes are sudden feelings of warmth that typically affect a woman's chest, neck, and face. They are sometimes accompanied by perspiration, followed by a chill, and occasionally by palpitations and anxiety. They occasionally last up to 30 min but typically last less than 5 min. Hot conditions, stress, or hot foods and drinks can occasionally bring them on. Hot flashes that happen at night are known as night sweats[4].

Physiology of menopause

There are essentially two phases to the menopausal transition, and it was first focused mostly on monthly patterns. However, these patterns now have hormone correlations. A slight rise in the incidence of the classic feature of menopause characterizes early menopause. However, the impact on menstrual cycles is minor because most women still have at least one period every 3 months. Several compensatory endocrine systems, notably increased follicle-stimulating hormone, work to keep the cycle going throughout this time despite the declining numbers of surviving follicles in the ovary. The comparison to subclinical thyroid dysfunction is appropriate since both conditions involve the increased release of trophic hormones while the thyroid gland works to maintain healthy T3 and T4 levels. As soon as a woman experiences an abrupt change, she shows a significant estrogen deficiency, making it impossible for ovarian failure to be addressed by adjustments in the production of ovarian and pituitary hormones. Increased signs typify this stage and herald the beginning of detectable bone mineral loss[5].

Old methods of treatment

Menopausal hormone replacement (MHR) therapy has been frequently used to address estrogen deficiency in female patients for over 50 years. Countless women started MHR and continued it for an extended period to treat symptoms of the VMS, such as hot flashes and nocturnal sweats, which began after menopause. Hormone therapy was assumed to offer preventive qualities and reduce vaginal symptoms such as dryness, irritation, itching, dyspareunia, and urinary sensations[6]. Exogenous estrogen was long believed to offer enduring cardioprotection, as shown by studies of longitudinal cohorts. However, neither the estrogen and progestin arm nor the estrogen-alone arm showed any advantage for cardiovascular disease. While breast cancer and venous thrombosis were previously mentioned as possible side effects of MHR[7]. Other therapies, including cognitive-behavioral therapy, herbal medicines, clonidine, gabapentin, and selective serotonin reuptake inhibitors, are ineffective or may cause side effects like drowsiness and nausea[8].

Fezolinetant

There is a significant need for a nonhormonal, safe, and effective medication for treating menopausal-related VMS. Antagonists of the neurokinin-3 receptor (NK3R) provide a unique treatment strategy. On 12 May 2023, the National Institutes of Health approved a unique type of drug, 'FEZOLINETANT (VEOZAH)', for treating menopausal symptoms such as hot flashes and nocturnal hyperhidrosis.

The central nervous system is the primary site of NK3 receptor (NK3R) expression, with a small amount of peripheral expression also found in the gastrointestinal tract, bladder, and reproductive tract[9]. The research that led to the development of fezolinetant, the first NK3R antagonist explicitly created to treat problems affecting women's health, was motivated by the finding relating human genetics to phenotype to understand the role of NK3R in the hypothalamic-pituitary-gonadal axis[10].

For treating moderate to severe menopausal VMS, the oral, nonhormonal drug fezolinetant is currently undergoing clinical trials. Fezolinetant, an antagonist of the neurokinin-3 receptor (NK3R), blocks NKB transmission, normalizing KNDy neuron activity in the brain's thermostat center and lowering VMS. It

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selectively blocks neurokinin-3 receptors. Even though kisspeptin, neurokinin B, and dynorphin co-express in specialized neurons known as KNDy neurons, the exact origin of VMS is still unknown. These neurons communicate with the hypothalamic thermoregulatory center and react negatively to estradiol's negative feedback. Hot flashes become more frequent as menopause continues and estrogen levels fall because of an increase in neurokinin B signaling at the KNDy neurons in the thermoregulatory zone. By preventing neurokinin B from attaching to KNDy neurons in the hypothalamus, fezolinetant lowers neuronal signaling and, as a result, the frequency and intensity of hot flashes. Although the exact mechanism of action is not fully elucidated, fezolinetant dampens neuronal activity and alleviates hot flashes[11,12].

Fezolinetant 90 mg BID significantly reduced moderate to severe VMS frequency and VMS score, which included frequency and severity, in a phase 2a clinical proof-of-concept study[12]. A phase 2b range of therapeutic dose investigation (VESTA) revealed that fezolinetant significantly decreased moderate to severe VMS frequency and intensity compared to placebo in perimenopausal women[13]. Fezolinetant was administered to most women (81–95%) and saw a 50% or higher drop in mild to severe VMS compared to baseline. The first week of treatment saw an improvement in VMS symptoms, which persisted throughout the whole 12-week period. This publication summarizes the findings of secondary endpoints from the VESTA project, including various specific treatment response definitions and the accompanying patient-reported outcomes (PROs). These PROs assessed how fezolinetant affected interference with daily activities caused by VMS and health-related quality of life.

In SKYLIGHT 1, menopausal women with moderate to severe VMS were compared to a placebo to assess the efficacy and safety of the novel nonhormonal treatment fezolinetant. With moderate to severe VMS (> 7 hot flashes per day), women between the ages of 40 and 65 were randomly assigned to receive either a once-daily placebo, fezolinetant 30 mg, or fezolinetant 45 mg. Co-primary efficacy outcomes included mean improvements in the frequency and severity of moderate-to-severe VMS from baseline to weeks 4 and 12. The evaluation of TEAEs (treatment-emergent adverse events)[14].

The SKYLIGHT 4 trial has provided evidence of the 52-week safety and tolerability of fezolinetant at doses of 30 mg and 45 mg, administered once daily. This trial, which was double-blinded and placebo-controlled, was explicitly designed to assess the long-term safety of fezolinetant. The results of this study will be presented orally at The North American Menopause Society Annual Meeting. Safety analyses conducted during the trial indicated that the incidence of endometrial hyperplasia and endometrial malignancy remained within the predefined limits for Fezolinetant. Patients who received the treatment reported TEAEs, most of which were of mild or moderate severity. The most common TEAEs observed were headache and fatigue, with similar incidences reported for both fezolinetant and placebo[15].

Headaches were a prevalent adverse effect, observed in ~9% of individuals using fezolinetant, comparable to the proportion of participants on placebo who experienced this symptom. However, the prescribing information contains a cautionary statement regarding increased levels of hepatic transaminase, indicating a risk of liver injury[16]. Severe adverse effects of this medication encompass persistent nausea/vomiting, loss of appetite, intense stomach/abdominal pain, yellowing of the eyes/skin, and dark-colored urine. While occurrences of a highly severe allergic reaction to this drug are infrequent, immediate medical assistance should be sought if any symptoms of an intense allergic response arise, such as a rash, itching/swelling (particularly of the face/tongue/throat), severe dizziness, or difficulty breathing[17]. Even though night sweats, hot flashes, and the sleep disruptions they cause are frequently dismissed as minor annoyances, they profoundly impact many parts of women's lives. Sleep, attention, mood, energy, and sexual activity are all disrupted for women who have seven or more moderate to severe VMS every day, which include sweating or functional impairment. Women seek treatment to improve their overall quality of life because the severity of VMS strongly correlates with how much everyday activities impair energy (77%) and procreation (61%). Women seek treatment to improve their overall quality of life because the severity of VMS strongly correlates with how much everyday activities impair women's health[18].

Conclusion

Hormone treatment may not be suitable for various medical conditions, including endometriosis before surgical menopause, enlarging fibroids, the use of certain medications, hereditary breast cancer risk, aura-tipped migraines, cardiovascular issues, stroke, venous thrombosis, and past endometriosis. Women with these conditions require more effective relief from menopausal symptoms than what nonhormonal therapies currently provide. Although the Institute for Clinical and Economic Review emphasized the need for long-term safety and efficacy data for fezolinetant, a neurokinin receptor antagonist, its development still significantly advances menopausal women's health[19].

A big step forward in women's health has been made with the FDA's approval of Veozah (Fezolinetant) as an alternative for menopausal symptom treatment. It can significantly reduce a woman's quality of life when she has hot flashes and nocturnal sweats, which are frequent menopause symptoms. Veozah has been given the go-ahead, giving women a nonhormonal therapeutic choice that is secure and efficient for managing these symptoms.

Veozah decreases the frequency and intensity of hot flashes and night sweats by inhibiting a specific receptor type in the brain. According to clinical research, Veozah is a successful therapeutic option with notable reductions in both the frequency and intensity of hot flashes and night sweats. Veozah is a popular treatment choice for many women due to its low risk of side effects. The FDA's clearance of Veozah, which offers a secure and efficient treatment alternative for menopausal symptoms, significantly advances women's health. A nonhormonal medication is available for women who experience hot flashes and night sweats, which can substantially enhance their quality of life during this transitional stage.

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